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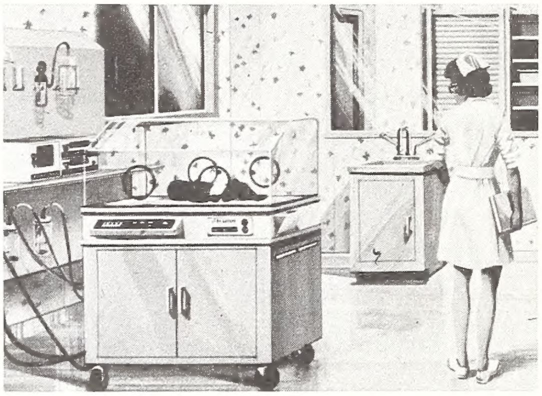
January 10, 1976



See page 25

RESEARCH ADVANCES:

NIH Scientist Describes New Dental X-ray Method........1
Investigator Is Unable to Find Increased Antigen Frequency..................7
Altered Gut Motility May Be Source of "Gas Pain".......9
Methods Sought to Reduce Damage to Heart Tissue...................................11
Heart Irregularity May Be Factor in Crib Death.............14
Antihistamine Drug May Be Useful in Treating Ulcers.........16

NEWS AND PHOTO FEATURES:

This Arthritis Therapy Might Be "Good as Gold".............18
NIH Scientists Find Subtle Defects in Cellular Immunity.....19
NICHD Opens Perinatal Center in NIH Clinical Center.........21

RESEARCH ILLUSTRATED:

Excellent Facilities Are Now Available in Perinatal Center..25

DISEASE PROFILE:

Progress Has Been Made Against Complications of Cystic Fibrosis..29

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Research Advances

NIH SCIENTIST DESCRIBES NEW DENTAL X-RAY METHOD

A scientist at the National Institute of Dental Research has described a new way to make dental radiographs. He believes that in many instances placing a shielded source of X-rays inside the mouth and the film outside is preferable to procedures now generally used.

Dr. Richard L. Webber, a clinician and physicist, believes this method reduced both the amount of radiation and the volume of tissue irradiated. He estimates that new high speed imaging systems, also using Polaroid film, can reduce the absorbed dose of radiation up to 50 times less than otherwise required; therefore, patient risk is reduced accordingly. Moreover, there is no need for the dentist to handle film packets contaminated with salivary bacteria.

The scientist points out that many routine diagnostic tasks permit the use of Polaroid film which saves time, and is more convenient to use in the dental clinic. The same basic system can be also used to produce panoramic radiographs.

Dr. Webber acknowledges that certain very demanding tasks such as the detection of small fractures or the discovery of incipient tooth decay in which the enamel defect is very small and hidden on a surface where teeth adjoin may not be performed reliably even when using conventional high-dose techniques. He says the maximum potential for dose reduction lies in the application of this system to other problems such as those routinely encountered in endodontics or orthodontics. By using less efficient films of the conventional type, the intra oral X-ray source

(more)

produces pictures of excellent quality having resolution comparable to that produced by conventional X-ray machines. Also, dentists sometimes use panoramic pictures to study the entire dentition. X-ray machines that take panoramic pictures differ from those most dentists now use routinely to study bone loss or locate cavities. The ideal diagnostic tool would be one machine easily adapted to all three purposes.

Dr. Webber's research team is working toward this end. They have put a lead shield over a pencil-shaped X-ray source produce by the Siemens company. A disposable, clear, plastic cover goes over the tube before each use. The machine is movable, and its position can be adjusted to many angles so that the tube can be inserted into the mouth while the patient's head is kept still and comfortable against an ordinary head rest. A window in the shield allows the investigators to direct a beam of light via a fiber optic bundle to the spot which they wish to study. In this way they make sure that the X-ray beam, which passes through the same window, is properly positioned for picture taking. Outside the mouth they place either a conventional film packet or a high speed cassette containing Polaroid film and a special reusable phosphor screen which intensifies the photographic effect of the X-rays. The choice depends on the type of diagnosis to be made and the amount of radiation required.

Dr. Webber says that operating this apparatus with Polaroid film is very simple. After switching on the X-ray machine to expose the cassette, the Polaroid film is processed by drawing the film packet between two rollers which evenly distribute the self processing chemicals.

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Fifteen seconds later he can examine a dry, finished print on the spot.

To get a panoramic picture, a different shield allows the X-rays to flow out in a semicircle. This irradiates more tissue, but less than with conventional machines having the source of radiation outside the head where its rays penetrate the entire skull.

At present there is no machine as versatile as the one Dr. Webber envisions, but the necessary adaptations appear possible. He points out that this technique would require dentists to employ an unfamiliar procedure, and to evaluate a positive rather than a negative picture. His preliminary survey indicates that most observers can identify a dental condition as correctly from one type of picture as from the other.

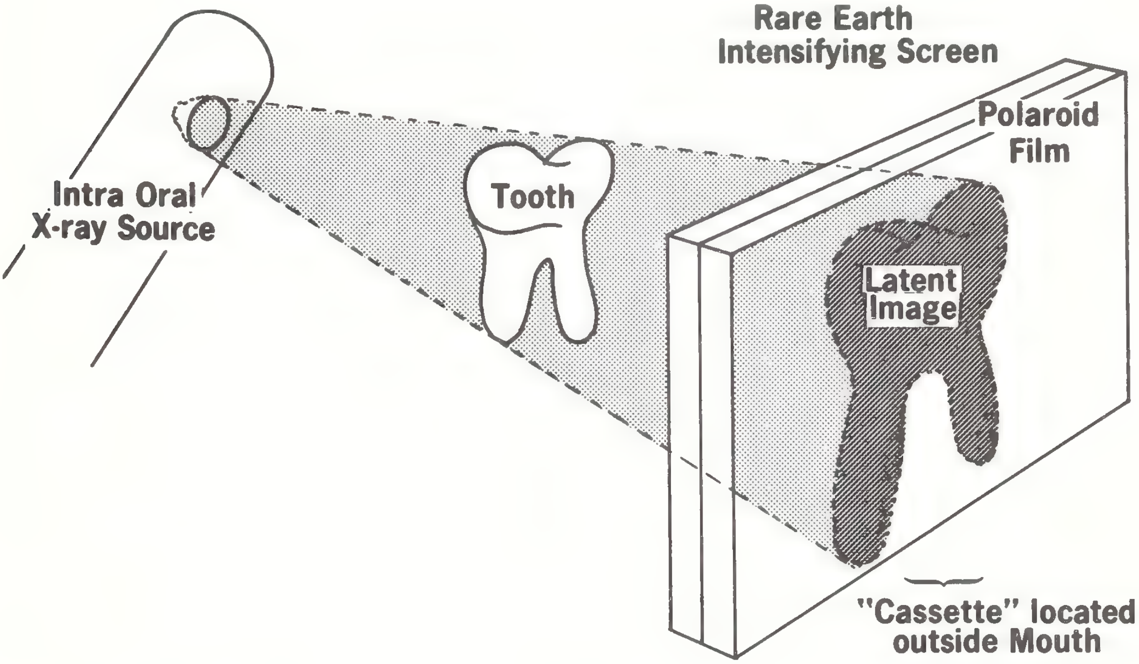
Another factor is the impossibility of exactly aligning the rays of an X-ray beam that close to its source. Therefore, divergent rays will distort the image somewhat, making near portions of an object appear larger than more distant ones. For many purposes this distortion does not interfere with diagnosis, according to Dr. Webber, who stresses that good diagnosis of any health problem requires that the risk of the method should be as little as possible and much less than the benefit of learning what the trouble is. Therefore, it would be preferable for dentists to tailor the type of X-ray technique to the requirement of an individual problem rather than to use a standard high-dose, high-resolution method for all occasions. In those instances where image distortion produced by divergence of the X-ray beam can not be tolerated, Dr. Webber suggests that the same basic X-ray source be moved outside the mouth and used in

(more)

DENTAL (Cont'd)

the conventional manner. In this way a single X-ray machine could be modified for use both intra orally and extra orally as the case demands. He and his associates hope that the reduced dosage for patients and increased convenience for dentists will encourage practitioners to explore this new technique.

Dr. Webber has published diagrams and illustrations of the experimental apparatus and its uses in the *Proceedings of the Society of Photo-Optical Instrumentation Engineers* 56:192-197, 1975. Another article on the subject by Richard L. Webber, D.D.S., Ph.D., in collaboration with William H. Schuette of the Biomedical Engineering and Instrumentation Branch, National Institutes of Health, Division of Research Services, and Willard C. Whitehouse, Chief of Television Engineering, National Institutes of Health, Clinical Center, appeared in *Oral Surgery, Oral Medicine, Oral Pathology*, October 1975.


Rare Earth Intensifying Screen
Polaroid Film
Intra Oral X-ray Source
Tooth
Latent Image
"Cassette" located outside Mouth

(NIH Photo #1511)

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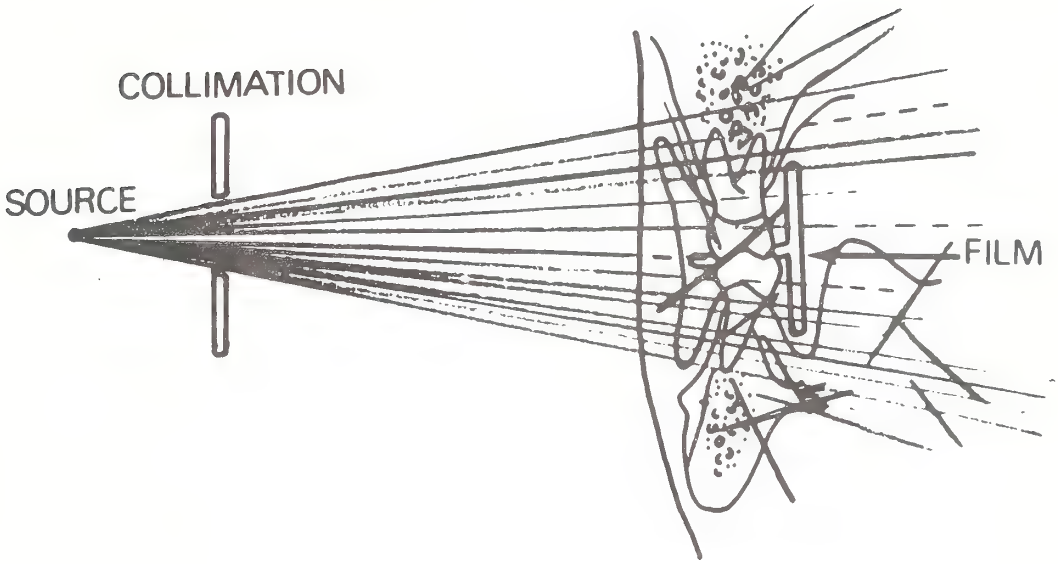
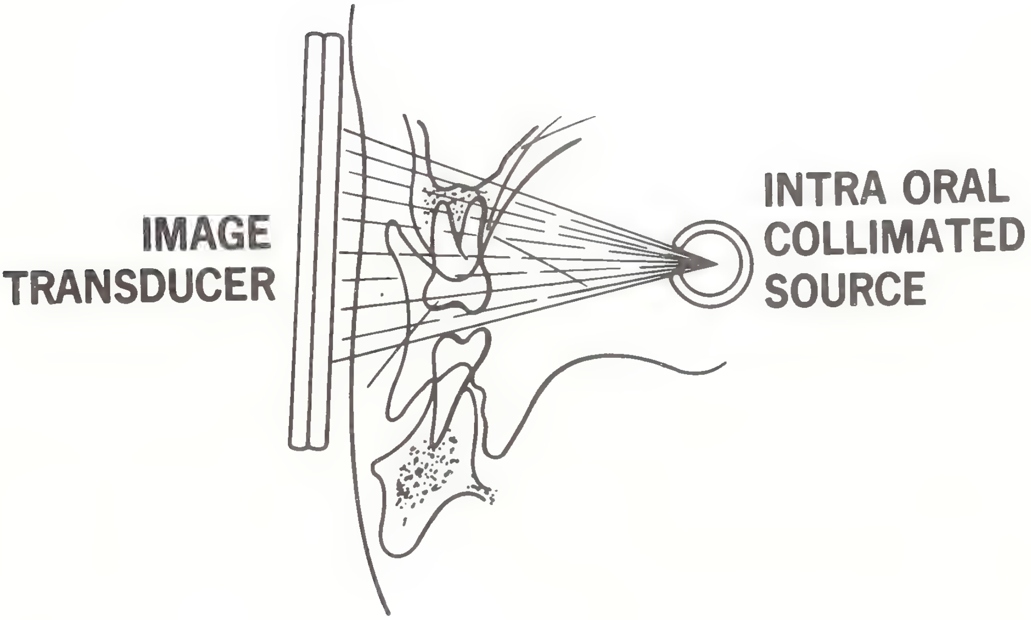
DENTAL (Cont'd)

CONVENTIONAL



PROPOSED ALTERNATIVE



These drawings compare the effect of geometry on the amount of tissue irradiated during conventional radiography (above) and during intraoral radiography (below) of interproximal lesions. (NIH Photos #1512 and 1513)

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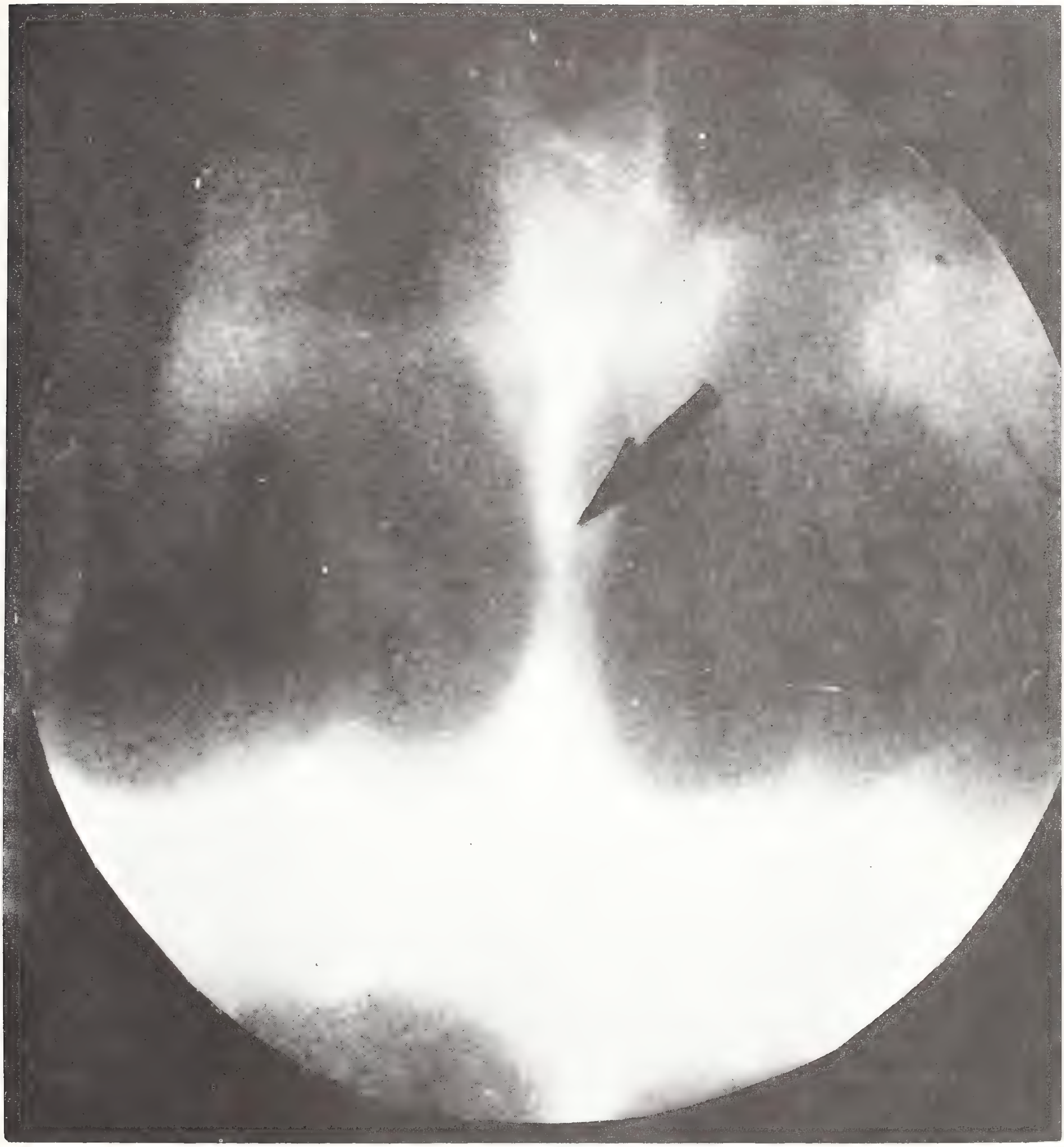
DENTAL (Cont'd)



This Polaroid radiograph produced from commercially available equipment shows a 1 mm^3 interproximal defect at the tip of the arrow. (NIH Photo #1514)

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Research Advances

INVESTIGATOR IS UNABLE TO FIND INCREASE IN ANTIGEN FREQUENCY

A Boston grantee of the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD), in one of the largest series of tissue typing in juvenile rheumatoid arthritis ever reported, has been unable to find an increased frequency of the histocompatibility antigen W27 in this disorder, as reported by a number of other investigators.

Recent studies have linked an increased frequency of the histocompatibility antigen W27 with ankylosing spondylitis, Reiter's disease, and acute anterior uveitis. In a 1973 study of 50 patients with juvenile rheumatoid arthritis (JRA) the present investigators were unable to link an increased W27 frequency with this particular disorder; however, a number of other studies have since reported such a link, suggesting that all of the aforementioned disorders may have a common etiology.

Therefore, the present investigators have again sought such a link in a long-term study of 123 patients with JRA. Their observations fail to support the contention of others that W27 is found more frequently than expected in patients with JRA. This discrepancy is attributed to the fact that the current investigators employed American Rheumatism Association (ARA) criteria for diagnosing JRA, which excludes both ankylosing spondylitis and Reiter's disease.

Using current ARA criteria for classifying JRA, each patient was reassessed annually regardless of disease activity, with a range of follow-up observation of one to 45 years. Those patients who ultimately

(more)

manifested characteristics of ankylosing spondylitis were dropped from the study. HL-A typing was performed by the microdroplet lymphocyte toxicity test for 30 HL-A antigens in the 123 patients and in 125 healthy control subjects.

No association could be found between any particular HL-A antigen and JRA. Although W27 was found in 15 percent of the patients and in only 6 percent of the control subjects, this difference was not statistically significant. One feature of JRA, tenosynovitis, was more common in the group with the W27 antigen than in those without it.

So, if there is a genetic factor involved in the cause of JRA, as suggested by other investigators, it does not appear to be associated with any of the HL-A markers, including W27, studied to date. NIAMDD grantee Dr. Peter H. Schur of the Robert B. Brigham Hospital, Boston, and associates reported their findings in the *New England Journal of Medicine*, September 25, 1975.

#

Research Advances

ALTERED GUT MOTILITY MAY BE SOURCE OF "GAS PAIN"

A Minnesota grantee of the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD) has shown, via objective measurements of abdominal gas volume, that complaints of bloating, pain, and gas attributed by affected patients to "too much gas" are due to altered gut motility and not to increased intestinal gas volume.

"Too much gas" causing abdominal pain and bloating is probably the most common gastrointestinal complaint encountered in medical practice. Lacking adequate objective measures of abdominal gas volume, medical science has generally accepted the patient's subjective assessment of his quantity of intestinal gas. So, the concept is widespread that excessive gas is a frequent cause of functional abdominal symptoms.

The investigators had previously determined the volume and composition of human intestinal gas by means of an intestinal washout technique. Using this same procedure they now have shown that patients with "too much gas" actually have a normal volume and composition of intestinal gas. Their studies indicate that complaints of bloating, pain, and gas may result from disordered intestinal motility in combination with an abnormal pain response to gut distention, rather than from increased volume of gas.

The relationship of gas to functional abdominal symptoms was studied in 18 patients with chronic complaints of excess gas and in ten healthy control subjects. The washout technique employed involves infusing an inert gas mixture (argon and sulfur hexafluoride) into the intestine of

(more)

the patients and control subjects, and collecting and analyzing the endogenous gas that is displaced.

Satisfactory washout curves, obtained in 12 of 18 patients, indicated that their mean intestinal gas volume (175 ml) did not differ significantly from that of control subjects (199 ml). Similarly, there was no difference in the composition (mostly nitrogen) or accumulation rate of intestinal gas. However, gas infused into the intestine of the patients produced much more discomfort than in normal subjects and had a greater tendency to reflux back into the stomach.

Moreover, six patients with such severe pain that gas infusions had to be terminated, had intestinal transit times of gas (40 minutes), which were markedly longer than those of control patients (22 minutes). The investigators suggest that efforts to reduce the volume of intestinal gas might benefit such patients, even though excessive gas is not their primary problem, as demonstrated in this study.

NIAMDD grantee Dr. Michael D. Levitt of the University of Minnesota and associates reported their findings in the *New England Journal of Medicine*, September 11, 1975.

#

Research Advances

METHODS SOUGHT TO REDUCE DAMAGE TO HEART TISSUE

Successful experimental efforts to reduce damage to heart tissue following a heart attack were described in California by a Boston physician whose research is funded in part by the National Heart and Lung Institute.

In a featured talk at the 48th Annual Scientific Sessions of the American Heart Association in November 1975, Dr. Eugene Braunwald, Head of the Department of Medicine of Harvard Medical School and Physician-in-Chief of the Peter Bent Brigham Hospital, reported on pioneering animal studies showing that heart-saving measures even when begun several hours after a heart attack can prove effective in limiting heart muscle injury.

This means that methods are now at hand with the potential to save the lives and improve the quality of life of many heart attack patients. Thus far, such novel treatment has been applied in only a few pilot studies in humans, but with highly promising results.

Dr. Braunwald developed the idea and then led pioneering efforts to learn the extent to which it is possible to salvage the compromised heart.

As Dr. Braunwald explained, the reduction in deaths in recent years has been attributable largely to the ability of coronary care units to detect potentially lethal heart beat abnormalities in time for physicians to restore normal rhythm. However, the mortality from "pump" failure, rather than erratic heart rhythm, has not declined significantly. In pump failure, the diseased heart is unable to muster enough contracting power to maintain adequate circulation to the body.

Studies had shown that patients who develop pump failure after a

(more)

heart attack generally have much larger areas of heart tissue damage and death than heart attack patients who do not.

It stood to reason, then, that any treatment which reduces the amount of heart tissue death would also offset the chances of the patient developing heart failure, thereby increasing his chances of survival.

The hitch, however, was that it had long been a widely-held tenet among medical men that once blood supply to portions of heart muscle was shut off because of blockades in the coronary arteries, nothing could be done. That oxygen-starved area of the heart was necessarily condemned to death.

In recent years, however, Dr. Braunwald and his associates launched studies to test whether extent of heart injury could be modified.

Towards this end, they devised a variety of new techniques to measure tissue damage in dogs undergoing experimental heart attack through repetitive closure of the coronary arteries.

Among these techniques was epicardial electrocardiography, by which electrical signals can be directly recorded from the surface of the heart, together with measurements of the amount of leakage of enzymes from damaged heart cells and chemical and detailed microscopic study of tissue.

From these studies, Dr. Braunwald said, "It became clear that for several hours following coronary occlusion (heart attack) the fate of substantial quantities of myocardium (heart tissue) is delicately poised. Relatively slight alteration in balance between supply and demand can

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influence the survival of large quantities of cardiac muscle."

In one set of trials, the investigators put extra demands on damaged hearts by means of tachycardia (more rapid heart beat), and this resulted in an increase in the severity of heart injury. In other experiments, they sought to alter the balance in the heart's favor. Using an auxiliary balloon pump to assume some of the workload of the heart, they were able to help the heart better meet its needs so as to reduce the extent of heart damage.

Other laboratories have since joined in these investigations and have discovered a number of promising ways of intervening to help protect the heart. These include a substance extracted from cobra venom, an agent called hyaluronidase, a brew made up of glucose, insulin and potassium, the compound hypertonic mannitol, corticosteroids, sublingual (under-the-tongue) nitroglycerin and balloon pumping. Some of these have been tested in pilot studies in humans, and the preliminary observations, according to Dr. Braunwald, are "exciting and encouraging."

#

Research Advances

HEART IRREGULARITY MAY BE FACTOR IN CRIB DEATH

An inherited heart irregularity seen in the electrocardiogram may help account for sudden, unexpected infant death, according to a report delivered in November 1975, at the 48th Annual Scientific Sessions of the American Heart Association.

The so-called Sudden Infant Death Syndrome (SIDS) or "crib death" is the largest single cause of death in newborns between one week and one year of age. It kills about 10,000 apparently healthy infants annually in the United States by mechanisms yet unknown.

However, a study by a team of scientists from the National Heart and Lung Institute now suggests that some cases of crib death may be caused by a specific inherited abnormality in the electrical signal that makes the heart beat. This irregularity has already been found to produce occasional fainting spells and even sudden death in children and adults.

The abnormality is defined as a "prolonged Q-T interval." This refers to an abnormal lengthening of a portion of the squiggly-lined electrical signal as recorded by the electrocardiogram and designated by the letters Q and T.

Suspecting a fault in the heart beat as a culprit, the investigators measured the electrocardiograms of 42 sets of parents who had at least one infant succumb to SIDS. They found 11 of the 42 sets of parents (26 percent) with "prolonged Q-T intervals" on the EKG, a proportion significantly higher than that observed in the general population. Moreover, in

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families with a parent demonstrating this prolongation, the same abnormality was observed in 40 percent of the siblings of infants who died suddenly. In addition, one infant with "near-miss" SIDS showed marked Q-T interval prolongation after an episode of cardiac arrest at seven weeks of age.

The investigators emphasized, however, that the data are still only suggestive. Definite confirmation of the link between Q-T interval prolongation and SIDS will require large, prospective studies.

Co-authors of the report were Drs. Barry J. Maron, Chester E. Clark, Robert E. Goldstein, Russell S. Fisher and Stephen E. Epstein.

#

Research Advances

ANTIHISTAMINE DRUG MAY BE USEFUL IN TREATING ULCERS

A Los Angeles grantee of the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD) has shown in preliminary clinical trials that cimetidine (Smith, Kline and French Laboratories), a recently-synthesized antihistamine drug, is a potent inhibitor of gastric acid secretion in patients with duodenal ulcer. This agent apparently is not toxic and, thus, may be useful in treating peptic ulcer disease.

Metiamide (Smith, Kline and French Laboratories) is a potent inhibitor of gastric acid secretion in duodenal ulcer patients. Use of this new type of antihistamine drug, however, or H_2-receptor antagonist, has been associated with development of a blood disorder, agranulocytosis, in two patients. Thus, because metiamide contains thiourea, which is known to produce agranulocytosis, agents have been sought which have a similar gastric acid inhibitory action, but which are devoid of this potential toxicity.

Cimetidine is a recently synthesized non-thiourea-containing H_2-receptor antagonist, which, in animal studies, has been found to be as effective as metiamide, and free of significant toxicity. The present studies have shown that cimetidine is markedly more effective than a popular anticholinergic drug in duodenal ulcer patients, that it does not produce acute side effects, and, thus, it may be of value in the treatment of peptic ulcer disease.

The effect of cimetidine on basal and meal-stimulated gastric acid secretion was studied in seven patients with duodenal ulcer. Oral doses of 100, 200, and 300 mg were tested. In addition, a comparison was made

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of the effects of cimetidine and of an optimally effective dose of propantheline bromide on meal-stimulated gastric acid secretion.

Each dose of cimetidine significantly inhibited basal and meal-stimulated gastric acid secretion. Basal acid secretion was abolished after a 300 mg dose, while meal-stimulated three-hour acid output was reduced 67 percent. These effects of cimetidine were dose-related, were positively correlated with blood cimetidine concentrations, and were not associated with clinical or biochemical abnormalities. A 300 mg dose of cimetidine decreased meal-stimulated acid secretion significantly more than an optimal effective dose of propantheline bromide.

Moreover, cimetidine was comparable in potency to metiamide, but had a longer duration of effect, and did not affect meal-stimulated gastrin release. Thus, cimetidine seems to be ideal as a potential therapeutic agent in patients with peptic ulcer disease, but this possibility must be tested in well-controlled, long-term clinical trials to rule out any possibility of adverse side effects.

NIAMDD grantee Dr. Jon I. Isenberg of the University of California, Los Angeles, and associates reported their study in the *New England Journal of Medicine*, August 21, 1975.

#

News Feature

THIS ARTHRITIS THERAPY MIGHT BE "GOOD AS GOLD"

Five million Americans are afflicted with rheumatoid arthritis, a disease with an underlying abnormality that is not limited to joints, but can affect any organ of the body.

Treatment in the early stages of rheumatoid arthritis is designed to relieve pain, to control inflammation, and to prevent deformity. Many cases can be controlled satisfactorily on a program of rest and physical therapy, using salicylate drugs such as aspirin, according to the National Institute of Arthritis, Metabolism, and Digestive Diseases.

In some cases, the disease subsides without intervention. In other cases, progressive joint damage cannot be stopped or slowed with rest and salicylates, or the process, having subsided, may flare up with each attempt to resume normal activity. Physicians have available a wide range of alternative drugs which--although they may be more effective in controlling the disease--are more likely to have toxic side-effects. One such substance is "gold salts."

John T. Sharp, M.D., of the Baylor College of Medicine, Houston, has shown by radiologic evaluation that gold therapy helps alter the course of rheumatoid arthritis in a group of patients given injections of a soluble gold compound for 20 to 30 weeks.

Weekly injections of 25 or 50 milligrams consist of about 50 percent elemental gold. Periodic radiologic examinations have shown the arrest of bone and cartilage destruction in several patients, as well as a significant slowing of the progression rate of joint damage for the treated group. Dr. Sharp is now exploring the relationship of blood levels of gold to changes in the patients' condition.

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News Feature

NIH SCIENTISTS FIND SUBTLE DEFECTS IN CELLULAR IMMUNITY

National Institutes of Health scientists have demonstrated subtle defects in the cellular immunity of the majority of apparently normal individuals who develop cryptococcosis, the most common cause of fungal meningitis. These defects probably existed prior to the infection and may have predisposed these persons to the disease.

Cryptococcus neoformans, a fungus commonly found in pigeon droppings, causes a respiratory infection often overlooked until it spreads to other areas of the body, particularly the central nervous system where it causes meningitis. This meningeal form of the disease is frequently seen in patients whose immune system has been impaired by either immunosuppressive treatment for a kidney transplant or by certain disease processes, such as leukemia, lymphoma, or sarcoidosis.

However, more than half of the cases of cryptococcosis occur in persons with apparently normal immune responses. Encouraged by earlier evidence of probably immunologic defects in such normal patients, the National Cancer Institute's Dr. Stephen C. Schimpff and the National Institute of Allergy and Infectious Diseases' Dr. John E. Bennett decided to measure the cell-mediated responses to these patients to mumps, tuberculosis, streptococcal, and cryptococcal antigens.

The researchers discovered a variety of cell-mediated defects in apparently normal individuals who had been cured of cryptococcal infections for at least one year. When small amounts of antigens were injected under the skin of these patients, they were found to have depressed immune responses to mumps and cryptococcin -- an antigen derived from the fungus

(more)

-- and possibly to strep antigens.

In a laboratory test, leucocyte migration inhibition, which measures a substance involved in cell-mediated reactions, the same group of patients exhibited abnormal responses to both the killed cryptococci and cryptococcin but normal responses, on the whole, to the other antigens. However, several individuals had impaired luekocyte migration inhibition responses to all of the antigens. This was also the situation in their responses to all five antigens as measured by a third test: lymphocyte transformation. Although the grouped responses were normal, individual values again indicated a variety of deficiencies.

The responses of normal patients not yet cured of cryptococcosis resembled those of the cured group. Patients with other diseases which altered their immune status responded very poorly in all the tests.

The continued presence of immunologic defects in patients cured of cryptococcosis for one year indicates that these persons are not "normal" and probably had these defects prior to the disease. This finding, along with the tendency of patients with compromised immune status to develop cryptococcosis, strongly implies that spread of *C. neoformans* requires a person deficient in certain aspects of cell-mediated immunity.

Drs. Schimpff and Bennett point out that these deficiencies cannot be predicted on the basis of one test alone. Although a few patients did respond abnormally to all the tests, most of them had a variety of deficiencies in various tests.

This study was reported in the June, 1975 issue of the *Journal of Allergy and Clinical Immunology*.

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NEWS & FEATURES From NIH January 10, 1976

News Feature

NICHD OPENS PERINATAL CENTER WITHIN NIH CLINICAL CENTER

Each year, approximately 50,000 infants in the United States die before they are 28 days old. Concern for the problems of the children, aided by research and planning, have led to the development of the new Perinatal Center at the National Institute of Child Health and Human Development (NICHD). Dr. Norman Kretchmer, NICHD Director, has announced that the Center, which is designed to provide care and conduct research on disorders of high-risk infants, has begun admitting babies.

"The Perinatal Center brings together a superb physical plant, laboratories, a staff, and the environment necessary to study, diagnose, and treat some of the more difficult problems in pediatrics," Dr. Kretchmer said. "These are the metabolic, nutritional, genetic, endocrine, and growth and development difficulties of infants, particularly of low birth weight infants. Our research is directed toward accelerating their growth and development in order to improve their chances for survival," he said.

Roughly half of the early infant deaths occur in low birth weight (LBW) infants. The problems of the LBW infant have two sources - either the infant was denied the growth spurt normal fetuses experience in the last 12 to 16 weeks before birth by premature delivery, or its rate of growth in the uterus was retarded. In general, the LBW infant's life support mechanisms are poorly developed and require elaborate equipment, such as incubators to regulate its body temperature, ventilators to maintain breathing, and sensitive devices to monitor heart rate, breathing and other vital functions.

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This specialized care and necessary equipment may not be available in many hospitals. Where it is available, hospital intensive care for a LBW infant has been known to cost as much as $80,000. The care and treatment provided by the Perinatal Center is free.

Infants that have LBW-associated problems, metabolic, or genetic disorders, are considered for acceptance at the Center upon the referral of a physician. Patients are brought to the nursery in transport incubators with a NICHD staff pediatrician accompanying the infant.

The brightly decorated nursery has no windows, and lighting is controlled in intensity. Air in the room is changed 20 times per hour and constant temperature and humidity is closely maintained. Incubators, equipped with monitoring instruments, regulate quantity, composition, humidity, and temperature of the breathing gases. They continuously follow heart rate, body temperature, and lung function. Ventilators are available to assist respiration.

The Center is scheduled to be equipped with the Clinical Center's computerized information system for gathering, transmitting, and storing medical information. The system will record and display physicians' orders, nursing plans, laboratory reports, admission and discharge data, and clinical research protocols.

The eighth floor contains research laboratories. Extremely small samples of blood and urine from the infants is sent here to be analyzed for diagnostic purposes. For example, with this equipment all 21 common amino acids, the protein building blocks of the body, can be measured in a few drops of blood or urine. Following diagnosis, frequent analyses

(more)

PERINATAL (Cont'd)

check the progress of treatments and indicate if there is a need to modify medication or to change special formulas containing dietary supplements.

Hospital rooms for mothers, infants, and children, visiting rooms for family members, and a nursing station are located on the ninth floor. Mothers may be admitted to the Center in studies of breast feeding and in infant-mother behavior studies.

In one recent case, physicians from a local hospital consulted with NICHD researchers about a baby who began to show several disturbances such as seizures, vomiting, and abnormally acidic blood within 12 hours after birth.

Blood and urine samples were sent to NICHD and subjected to tests which determined the chemical abnormality causing the disturbance. Investigators working with NICHD biochemical geneticist Dr. Joseph Schulman discovered the baby showed an inborn error of metabolism, identified as pyroglutamic aciduria. The disorder is a genetically-caused overproduction of pyroglutamic acid, a normal product of cell metabolism.

When therapy for the disorder was initiated, the baby's condition improved and he was discharged from the hospital at 12 days of age. Without such treatment, the condition is extremely serious and may be lethal. Not only did the researchers probably save this baby's life, but also the lives of future babies who may suffer from this rare disorder. By growing small samples of the baby's skin cells through a technique called tissue culture, the cells can be maintained for years to come, enabling researchers to observe the specific effects of the alteration of metabolism occurring from absence of the enzyme glutathione synthase.

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New therapeutic techniques and insight into the function of particular metabolic pathways may result from his treatment.

Though the Perinatal Center may treat a limited numbers of patients, the work that it performs may lead to treatments for a number of infantile disorders. Through research, therapy for previously incurable and sometimes fatal diseases can be established and applied throughout the country.

For example, knowledge derived from research upon hyaline membrane disease, a fairly common lung disorder which could not be effectively treated prior to 1971, has led to successful methods for diagnosis and treatment. Through these efforts the Perinatal Center will help NICHD take one more step towards lowering infant mortality.

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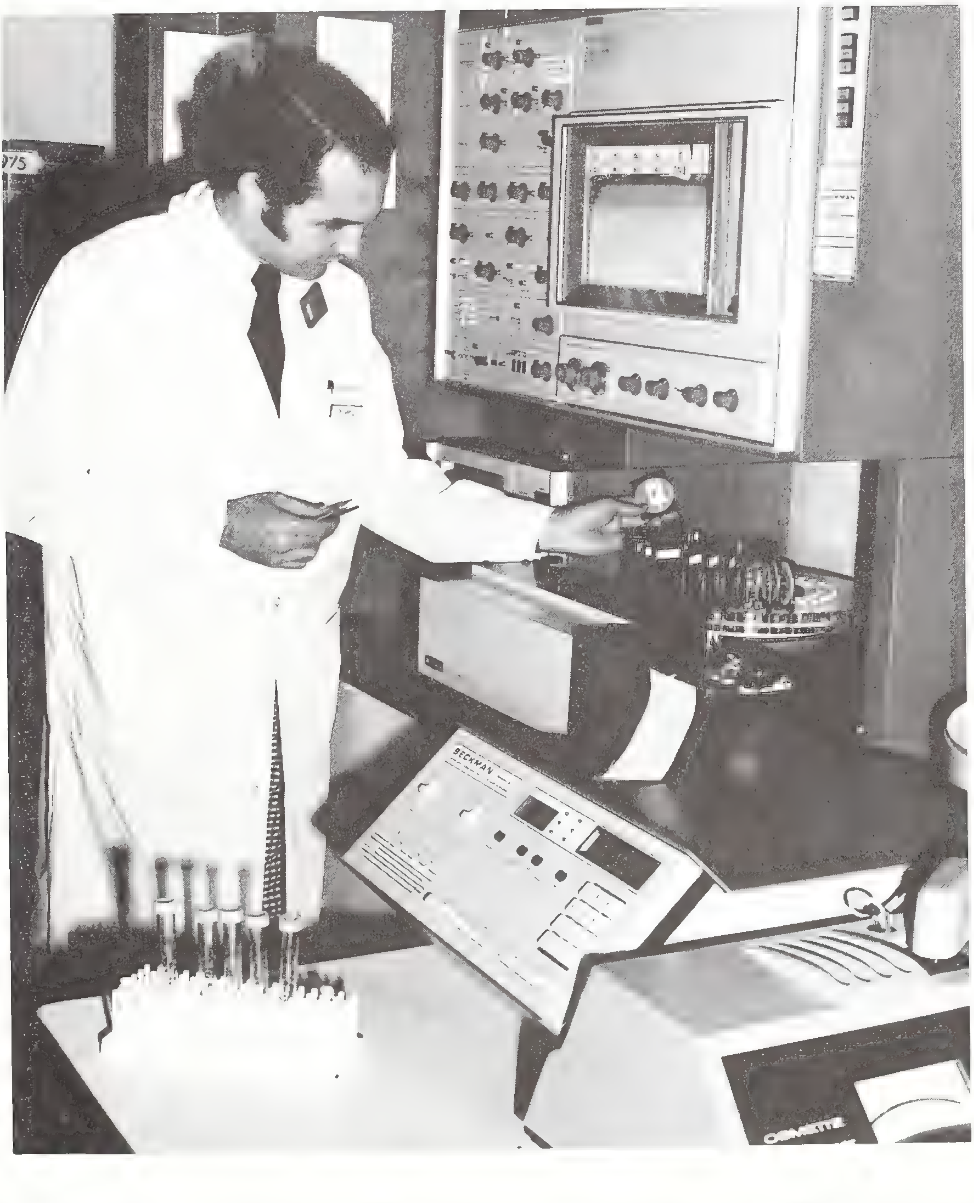
OF RELATED INTEREST
are the photographs
which appear in the
Research Illustrated
section that follows
this story.

Research Illustrated

EXCELLENT FACILITIES ARE NOW AVAILABLE IN PERINATAL CENTER



Dr. Philip Farrell, Chief of the National Institute of Child Health and Human Development's Neonatal and Pediatric Medicine Branch, places a sample coil containing plasma from a newborn in an automated amino acid analyzer. Samples of 0.1 ml of blood or urine are processed automatically through ion exchange columns for measurement of all 21 common amino acids. Final results appear on printed tapes within three hours. (NIH Photo 1515)

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Dr. Philip Farrell, NICHD Chief of Neonatal and Pediatric Medicine Branch, checks tissue culture flasks containing fibroblasts from a 1 mm skin biopsy taken from a newborn with metabolic disease. Cells reproduce in the flasks, and cultures are maintained indefinitely for biochemical studies. (NIH Photo 1516)

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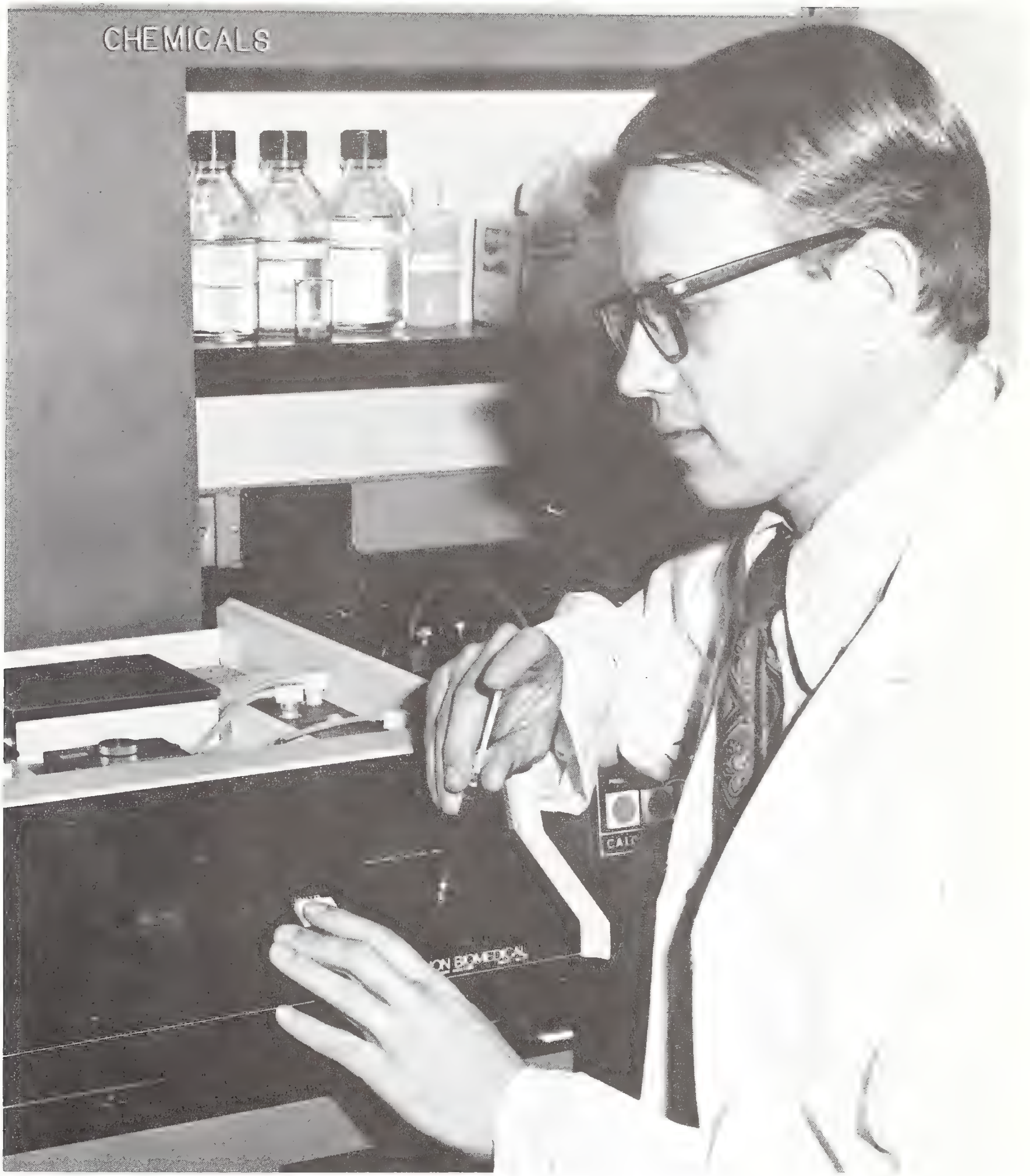
RESEARCH ILLUSTRATED (Cont'd)



Dr. James Hansen, NICHD neonatologist, determines the ionized calcium content of a blood sample from a premature baby, using an automated electrode procedure. The instrument measures calcium on less than one-half ml of whole blood. (NIH Photo 1517)

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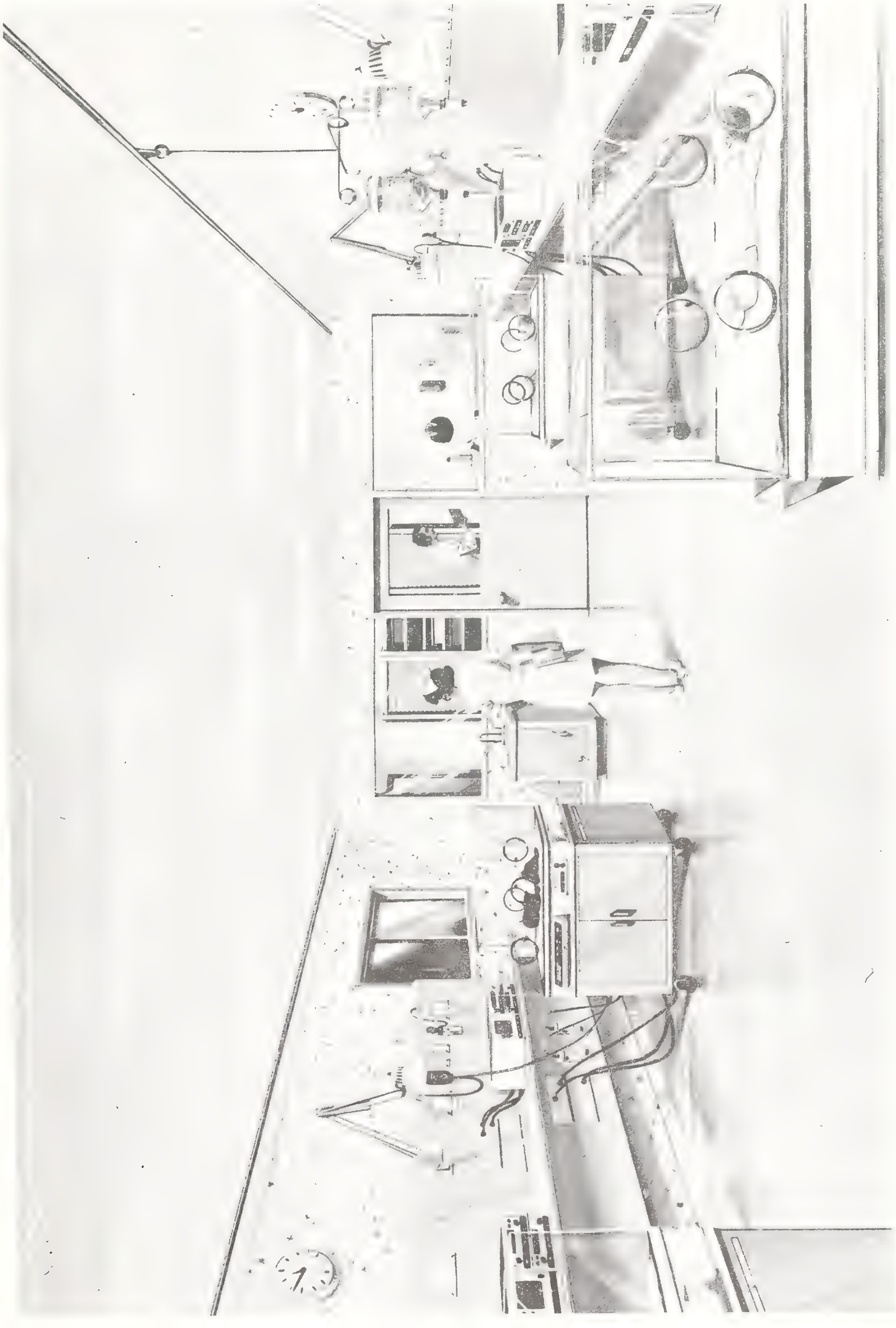

The Special Care Nursery of the NICHD Perinatal Center is designed to provide care and treatment of newborns, and is one of the foremost facilities of its kind. (NIH Photo #15[illegible]8

#

Disease Profile

PROGRESS HAS BEEN MADE AGAINST COMPLICATIONS OF CYSTIC FIBROSIS

Although much still remains to be learned about cystic fibrosis (CF), the clinical picture of this inherited metabolic disorder of exocrine secretion is brighter now than in years past. The exact nature of the basic chemical defect in CF still eludes investigators, but great strides have been made in alleviating the complications of the disease.

Striking one in every 1,500 infants, cystic fibrosis is characterized by malfunctioning exocrine glands that secrete abnormal fluid to internal and external body surfaces, particularly to the gastrointestinal and respiratory mucosal linings and the skin.

Research conducted and supported by the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD), is aimed specifically at defining the physiologic effects of the clinical manifestations, at determining the biochemical aberrations associated with the disease, and at developing improved methods of prompt diagnosis, more effective treatment, and hopefully, eventual prevention of this disease.

In addition to investigations carried out at National Institutes of Health laboratories and clinics in Bethesda, the NIAMDD supports many cystic fibrosis research projects at medical centers and institutions across the country through the research grant mechanism.

Cystic fibrosis results in three principal clinical problems. The first is the production of sweat with a high salt content. Because of this defect, patients are unable to conserve salt and are therefore at risk of developing profound dehydration or heat exhaustion in the summer, either of which may be fatal.

(more)

The second is that in CF the mucus-secreting glands of the body fail to secrete normal, clear, free-flowing fluid. Instead, they produce abnormally thick, viscous mucus which tends to obstruct the ducts or openings of these glands. When the mucus accumulates in the ducts of the pancreas, it interferes with the ability of this gland to supply digestive enzymes to the intestinal tract, thus leading to poor digestion of food and to malabsorption of a number of essential nutrients. Depending on the severity of this complication, the patient may suffer from general underdevelopment, poor musculature, and retarded bone growth.

The third and most serious complication is the development of progressive, chronic lung disease. Thick mucus obstructs the smaller air passages in the lung, causing labored breathing and chronic cough. In time, bacteria multiply in the accumulated secretions, predisposing the child to chronic bronchitis or pneumonia - a leading cause of death in these patients. The lung changes may also restrict pulmonary blood flow, leading to increased blood pressure in the lung and to consequent chronic heart strain and eventual heart failure.

Many NIAMDD-supported research projects in CF are related to applications of existing medical knowledge to improved treatment, while other more basic studies involve the search for a specific biochemical defect or genetic abnormality responsible for the disease. Some projects have implications for improving tests for early diagnosis (or developing new ones), for elucidating the specific mechanism of exocrine gland dysfunctions, and for determining the nature of the molecular defect in cell components.

A prime factor in the management of this disease is to establish a

(more)

correct and early diagnosis prior to the development of irreversible pulmonary complications. The most widely used diagnostic test, based upon an abnormally high concentration of salt in sweat, illustrates one of the manifestations of exocrine gland dysfunction. A number of research projects are concerned with secretory mechanisms, including those of the sweat glands, salivary glands, and those of the respiratory and gastrointestinal systems.

A disease of many disguises, CF offers only enigmatic clues to the disorder's basic mechanism. Promising findings in fundamental research and innovative methods of diagnosis and treatment, however, have opened up new avenues for investigation, resulting in a somewhat more optimistic outlook for patients.

#

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See page 19

RESEARCH ADVANCES:

Alcohol Abuse Leads to Liver Damage, Regardless of an Otherwise Good Diet.........1
C-AMP Might Trigger Jawbone Cell Changes................3
Monkey Virus May Be Model for Study of Human Virus........7
Cleft Palate Defect Linked to Drugs Taken During Pregnancy...................9

NEWS AND PHOTO FEATURES:

Nuclear Spectrometer Available at Stanford University......13
Keto Acids Can Serve as Dietary Supplement for Kidney Patients...16
These Twin Monkeys Are a Rare Pair.........................19
Asphyxia During Pregnancy Can Cause Brain Damage...........20
Prostaglandin Deficiency in Kidneys Might Be a Cause of Hypertension..................................21
Cancerline Provides Easier Access to Cancer Information....22

RESEARCH ILLUSTRATED:

Babies' Hearing Assessed by New Behavioral Technique.......24

DISEASE PROFILE:

Cause of Parkinson's Disease Is Unknown...................28

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Research Advances

ALCOHOL ABUSE LEADS TO LIVER DAMAGE, REGARDLESS OF AN OTHERWISE GOOD DIET

Alcoholics should not be led to believe that correction of nutritional deficiencies will prevent liver damage, said Charles S. Lieber, M.D., in a position paper based on seven years of research supported by the National Institute of Arthritis, Metabolism, and Digestive Diseases.

Dr. Lieber found that alcohol exerts direct toxic effects on both the liver and gut, resulting in structural alterations in cells of the intestine, and in successive development of fatty liver, alcoholic hepatitis, and cirrhosis.

Alcoholics, said Dr. Lieber, often are malnourished because alcohol displaces protein-, vitamin-, and mineral-containing foods in the diet, and chronic alcohol consumption eventually may result in malabsorption of some essential nutrients. In his early studies, the investigator showed that rats develop a fatty liver when fed ethanol as part of a nutritionally adequate diet; subsequently, he duplicated these findings in monkeys and in normal and alcoholic volunteer human subjects.

His studies have revealed that liver injury is preceded by an adaptive phase characterized by accelerated metabolism of drugs (including ethanol), ketonemia and hyperlipemia followed by accumulation of fat in liver cells, secondary to hypertrophy and hyperactivity of the smooth endoplasmic reticulum. Side effects include enhanced hepatotoxicity of other noxious agents, such as carbon tetrachloride and possibly energy wastage.

Finally, Dr. Lieber showed that fatty liver produced by ethanol can progress to alcoholic hepatitis and cirrhosis despite a nutritionally adequate

(more)

diet. Baboons were fed a nutritionally complete diet in which ethanol isocalorically replaced carbohydrate and accounted for 50 percent of the total calories. All 15 animals developed fatty liver within nine months time, five exhibited typical alcoholic hepatitis, and five baboons studied for two to four years developed cirrhosis.

The Mount Sinai School of Medicine investigator summarized his findings in a special communication to the *Journal of the American Medical Association*, Vol. 233, No. 10, September 8, 1975. Dr. Lieber's paper was commissioned by the Council on Foods and Nutrition of the American Medical Association.

#

Research Advances

C-AMP MIGHT TRIGGER JAWBONE CELL CHANGES

Levels of a cyclic nucleotide called C-AMP (cyclic adenosine 3'5-monophosphate) nearly doubled in the jawbones of animals whose teeth were pressured for four weeks by wire springs, according to University of Pennsylvania scientists whose work is supported by the National Institute of Dental Research (NIDR).

The scientists believe that C-AMP, a chemical that responds to hormonal administration, could be the "second messenger" triggering bone cell change in a two-step response to orthodontic pressure. They suggest that further investigation of possible "first messengers" (hormones, prostaglandins, or electric current) might lead to ways to hasten knitting of broken bones, and correction of misaligned teeth.

Zeev Davidovitch, D.M.D., and Joseph L. Shanfeld, Ph.D., at the University of Pennsylvania's School of Dental Medicine, wondered whether C-AMP might convey a message from points of physical pressure to nearby bone cells. To test this hypothesis, they fastened wire springs to cats' canine teeth on one side of the mouth in both upper and lower jaws. They adjusted the springs to pull the crowns of the teeth backwards. The corresponding teeth on the other side served as controls. At intervals from one hour to 28 days thereafter, the animals were studied in detail. Blocks of tissue from four areas of bone around each tooth were removed, analyzed, and compared for the presence of C-AMP.

Two areas were from the crest of the alveolar ridge of the jawbone and two were from the base of the tooth socket. In the blocks where

(more)

springs were placed, half the specimens had been under pressure and showed bone resorption, the other half were under tension and showed bone apposition.

The investigators found more C-AMP around the stressed teeth than around control teeth. They also found more C-AMP in crest sites than at the bases of teeth, and more in upper than in lower jaws. However, the amount was fairly equal in both compression and tension areas.

Levels of C-AMP changed with time. For the first day, the amount of C-AMP in all areas of both stressed and control teeth dropped slightly. It rose the following day, but more in stressed than control teeth. Thereafter, the levels fell again. By the end of the first week, C-AMP had dropped to about the level of the first day's fall. However, for the final three weeks of the experiment, levels in control areas rose slightly almost to their original state, whereas levels in the pressure areas rose steadily to twice that found at the start.

The scientists believe that the early reduction of C-AMP in compression areas was caused by cell death, while they attribute that in tension areas to cell growth.

The response of C-AMP to orthodontic pressure is much slower (two weeks) than the hormone-triggered C-AMP response. The scientists suggest that this may be because only those cells directly compressed respond, whereas hormones affect many more cells. However, the investigators believe that C-AMP is linked to both bone resorption and apposition since it appears almost equally in both areas. They cannot determine why more C-AMP develops at the crest of the jawbone than at the bases of teeth,

(more)

and why there is more in upper than lower jaws. Neither do they know the nature of the "first messenger" which triggers the synthesis of C-AMP.

The scientists believe that one could move teeth and make broken bones knit more rapidly than at present if a "first messenger" which increases C-AMP locally could be found. Perhaps a prostaglandin or an electric current might serve this purpose.

These findings were reported in *Archives of Oral Biology*, September 1975.

(more)

Wires apply pressure to this animal's canine teeth, causing a doubling of C-AMP in the jawbone. Cyclic nucleotides such as C-AMP serve as a second messenger, transmitting information from the exterior of the bone cell to the interior, triggering cells to remodel. Zeev Davidovitch, D.M.D., and Joseph L. Shanfeld, Ph.D., of the University of Pennsylvania's School of Dental Medicine, foresee the use of potent bone cell activating agents to remove old bone or produce new tissue locally. This research is supported by the National Institute of Dental Research. (NIH Photo #1519)

#

Research Advances

MONKEY VIRUS MAY BE MODEL FOR STUDY OF HUMAN VIRUS

Scientists in work supported by the National Institute of Allergy and Infectious Diseases have studied the Delta herpes virus (DHV) of patas monkeys and varicella-zoster (V-Z) virus of man and found a close relationship. They now believe it is possible DHV can be used as an animal model system for investigations of the human virus.

Varicella-zoster, like DHV, belongs to the herpes virus family. In children, V-Z causes chickenpox but, in some older persons, the same virus produces the condition known as "shingles." The latter occurs only if the affected individual has had chickenpox earlier in life and if the virus has since lain dormant in his body. How and why this latency and reactivation occur is not completely understood.

DHV causes a severe chicken-pox type of disease in patas monkeys and, in 1968, was responsible for an epizootic at the Delta Regional Primate Center, Covington, Louisiana where the virus was first isolated. At that time, no cross-neutralization between DHV and V-Z could be found. In 1973 when a second outbreak occurred, further studies were initiated and a serological relationship between DHV and V-Z was demonstrated by immunofluorescence.

In the latest studies by Dr. Ambhan D. Felsenfeld of the Primate Center and by Dr. Natalie J. Schmidt, State of California Department of Health, Berkeley, a new plaque reduction method was used to assay a neutralizing antibody to DHV and V-Z. Sera from eight animals associated with the 1968 out-

(more)

break and from three California V-Z patients were examined.

By both neutralization and complement fixation tests, a very close relationship between the two viruses was demonstrated, suggesting that DHV is actually a varicella virus of the patas monkey. In addition, the fact that immunization or infection with DHV or V-Z virus resulted in seroconversion to both viruses suggested a primary antibody response rather than recall of antibody elicited by prior infection with a related virus.

Although DHV and V-Z virus were found closely related immunologically, there are biological differences. V-Z virus replicates well in human cell strains and less readily in monkey cell cultures. DHV grew almost exclusively in the latter. Attempts to produce disease in patas monkeys with V-Z virus have been unsuccessful; however, susceptibility may be related to whether the animals had experienced previous infection with DHV.

Drs. Felsenfeld and Schmidt hope that the close immunological relationship demonstrated will enable them to use DHV for studies on the latency and reactivation of V-Z virus and, possibly, as a challenge virus in studies on the immunogenicity of experimental V-Z vaccines. This work was also supported by the Division of Research Resources, and was reported in the August 1975 issue of *Infection and Immunity*.

#

Research Advances

CLEFT PALATE DEFECT LINKED TO DRUGS TAKEN DURING PREGNANCY

Cleft palate, one of the most common birth defects, may be caused by drugs that interfere with fetal movements at the time the palate should be closing, according to animal studies by Bruce E. Walker, M.D., Ph.D., and others working at Michigan State University (East Lansing).

The scientists, whose work is supported by the National Institute of Dental Research, tested barbiturates, tranquilizers and anti-inflammatory drugs on pregnant mice, and photographed movements of the unborn mouse pups while still attached to the dam (see below). Their research was suggested by statistics indicating that epileptic mothers taking anticonvulsant drugs, and other pregnant women on barbiturates or tranquilizers, are somewhat more likely to have babies with clefts and other defects than women who have taken no drugs in early pregnancy.

(NIH Photo #1520)

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The investigators note that in the early stages of development of mammals, the tongue lies between two shelves of tissue on either side of the oral cavity and keeps them propped apart in a vertical position. Later the tongue drops, the shelves turn horizontally, grow out, touch, and finally fuse. In humans, the tongue still blocks this movement at six weeks. Between eight and ten weeks, however, the shelves fuse.

In mice, the shelves fuse approximately 15 days after conception. Dr. Walker's team found that if fluid is removed from amniotic sacs during days 13 and 14, the mouse cannot move freely, and the tongue may remain as a barrier until after the time for fusion has passed. However, when the scientists surgically released such mouse pups into a warm bath of culture fluid at day 15 and excised the tongue, they found that several hours later many of the shelves had turned and begun to fuse. Therefore, the potential for fusion seems to last some hours longer than the period in which it usually takes place, although in time this potential is lost.

Different strains of mice mature at different times and also react differently to drugs, Dr. Walker found. In the A/J strain, from 6.0 to 16.6 percent of the offspring spontaneously develop clefts, whereas strain CD1 has fewer clefts, and strain C3H rarely has any. The palatal closing time for CD1 mice is about one day earlier than for A/J mice.

In early experiments, the scientists administered several barbiturates and tranquilizers separately and in combination to pregnant mice of these three strains in order to keep them sedated during their normal hours of shelf fusion.

CD1 pups were examined at 16 days, and A/J pups at 17 days after their

(more)

mothers were treated. The researchers found that tranquilizers kept the animals quiet longer and caused fewer fetal deaths than barbiturates. Only chlorpromazine caused appreciable retardation of pup development. Cleft lip with cleft palate occurred in about ten percent of the A/J pups but not in the other strains. It also occurs spontaneously in the A/J strain. Cleft palate without cleft lip occurred in 21.6 percent of A/J, 13.6 percent of CD1, and 1.6 percent of C3H pups of mothers treated with chlorpromazine.

Barbiturates alone or with tranquilizers caused cleft palates in about 14 percent of the offspring. These drugs were most damaging when given one to three days before rather than on the day that closure usually begins. Phenobarbital and hydroxizine caused more clefts than the other drugs, and pentobarbital and diazepam caused the fewest, but all the drugs tested significantly increased the rate of clefting in all the strains.

Since many drugs, which act on the neuromuscular system of the dam, such as curare, do not cross the placenta sufficiently to paralyze the offspring, the investigators questioned whether these drugs were directly affecting the fetuses. Therefore, they devised a way of observing the pups. They anesthetized the dams below the third thoracic vertebra and fastened them to a support before suspending them in a warm bath. They surgically delivered the pups into this bath but left them still attached to the mother. Thus, the pups were able to develop for hours while being inspected. The movements of limbs, body, head, and sometimes of the tongue were timed and compared.

In one study of anti-inflammatory agents, the scientists found that four consecutive daily doses of triamcinolone (0.0175 mg) resulted in a large number of cleft offspring but few fetal deaths and few normally closed palates.

(more)

Cortisone injections caused considerable fetal death especially in A/J mice, but not in offspring of crosses between A/J males and C57BL females.

Triamcinolone given to mothers clearly reduced movement in the offspring. Cortisone reduced the activity even more in offspring of A/J dams. Movements of the hybrid offspring were somewhat reduced on day 14, but returned to levels similar to those of untreated pups by day 15.

Most movements were made by waving limbs, while other movements involved lifting the head from the chest and stretching and twisting the entire body. Usually the jaw remained open, but head movements opened it wider. The tongue was generally hard to see, but sometimes moved visibly. All movements increased in frequency as the fetus developed with time, but the offspring of treated A/J mothers were most retarded both in development and movement.

There was a correlation between the lack of movement caused by drugs and the occurrence of clefts. All the A/J pups whose dams were treated with cortisone had clefts, but some offspring of those treated with the less quieting triamcinolone developed normal palates. Hybrid pups whose mothers were treated with either drug had more clefts than control pups of untreated mothers, but fewer than drug-sensitive A/J pups. Hybrids also developed faster.

All of these experiments, according to Dr. Walder, indicate that tranquilizers and anti-inflammatory drugs, perhaps through a generalized effect on the neuromuscular system, delay movements that normally pull the tongue out of the way and allow palatal shelves to meet and fuse during a critical and limited period of development.

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NEWS & FEATURES From NIH February 10, 1976

Photo Feature

NUCLEAR SPECTROMETER AVAILABLE AT STANFORD

A new national center with one of the world's most powerful nuclear magnetic resonance spectrometers (NMR) is now available to molecular structure researchers.

The Stanford Magnetic Resonance Laboratory, located in the Chemistry Building at Stanford University's Medical Center, has been established by a joint grant from the NIH's Division of Research Resources Biotechnology Resources Program, and the National Science Foundation.

The new facility, directed by Dr. Oleg Jardetzky, will serve as a national biotechnology resource to aid scientists in their efforts to understand and conquer disease. The powerful NMR will make it possible for researchers to observe the magnetic properties of atoms in a molecule and provide information which describes their spatial relationships and movements.

For example, a scientist may label amino acids (the building blocks of proteins) with stable isotopes, and, from NMR specta, chart the changes in protein structure which result from the interaction with drugs or other chemical agents.

Stanford's NMR was built to operate at the highest frequencies that could be attained with available technology, Dr. Jardetzky said. The instrument has a resolution of 360 MHz (Mega Hertz) for hydrogen nuclei, and 90 MHz for carbon-13. Currently, abnormally shaped proteins associated with hereditary disease are being studied.

(more)

SPECTROMETER (CONT'D)

A scientist can follow the changes of shapes and motions of molecules with the added dimension of time. The NMR spectra can be blipped out into the screen every few seconds, and the memory of each spectrum is then stored in a computer. No other instrument can do this. Many things about dynamic movements of molecules can be inferred from these studies. According to Dr. Jardetzky, a model of a live and working protein can now be developed.

Other methods of studying proteins, he said, require that they be frozen or otherwise killed for measurement. The NMR method, however, measures molecules in solution without being damaged.

In addition to the study on the geometry of protein molecules, other specific projects to be undertaken include the examination of mechanisms of genetic control, cell membranes, and drugs and their effect on enzymes.

(more)

SPECTROMETER (CONT'D)

The first of the world's most powerful nuclear magnetic resonance spectrometers to aid scientists in their study of biological molecules and their role in life processes has been installed at Stanford University. Established by a joint grant from NIH's Division of Research Resources and the National Science Foundation, the new instrument allows scientists to "look" at individual atoms in complex structures. Dr. Oleg Jardetzdy, director, (left) consults with Woodrow Conover, operations manager, as research associate Norma Jardetzky operates the computer console. At extreme left is the 85K Gauss magnet--the heart of the high-resolution nuclear magnetic resonance spectometer operating at frequencies of 360 Mega Hertz. (NIH Photo #1521)

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February 10, 1976

News Feature

KETO ACIDS CAN SERVE AS DIETARY SUPPLEMENT FOR KIDNEY PATIENTS

A dietary supplement of keto-analogues of essential amino acids can postpone the need for dialysis, lengthen the period between dialysis, or temporarily take patients off dialysis, according to clinical researchers at the Johns Hopkins General Clinical Research Center (GCRC).

Clinical trials conducted by Drs. Mackenzie Walser and William E. Mitch at the Division of Research Resources-supported GCRCs have established that the dietary supplement decreases the load of nitrogenous waste required for excretion by the kidney.

The researchers have determined that keto acids could serve as building blocks for protein, and that under these conditions there is a marked conservation of nitrogen by the body.

It is estimated that approximately 60,000 people die each year in the United States with renal failure. Most could have been helped by hemodialysis, an artificial means of removing waste from the blood normally removed by the kidneys when they are functioning properly.

At present, there are about 16,000 patients receiving dialysis, which is expensive (approximately $125 per treatment), inconvenient, and time-consuming.

Because metabolism of nitrogen in the body begins with dietary intake of protein and ends up with renal excretion of urea, the Johns Hopkins scientists have concentrated their efforts in improving the efficiency of the transamination process in the body. Transamination is actually a recycling process which transfers nitrogen (in liver and muscle) from non-

(more)

essential amino acids, and also adjusts levels of individual amino acids to tissue needs.

In most cases this treatment has postponed the need for dialysis by renal patients for months by reducing urea production--and in some cases by slowing down the progression of the renal deterioration.

In a most recent GCRC outpatient study, seven renal failure cases were treated with the keto acid diet. One of the seven had been on dialysis twice a week for five months. The other six were considered prime candidates for immediate dialysis.

By subsequent keto acid therapy, six of the patients were maintained for an average period of six months before dialysis had to be instituted or reinstituted. The seventh patient remains completely off dialysis after more than one year.

None of the group developed any of the usual signs of renal incompetence or uremic poisoning, including peripheral neuropathy, premature atherosclerosis, renal osteodystrophy, or lowered bone density. Three of the seven had shown reduced nerve conduction velocity prior to treatment. This improved during keto acid therapy in two of the three. Three patients also showed a reduction of previous high plasma triglycerides to values within the normal range.

The keto acids used in these clinical tests were actually synthesized at the Johns Hopkins University School of Medicine. It is speculated that the cost of this production will be greatly reduced when the pharmaceutical

(more)

DIALYSIS (CONT'D)

and chemical industries begin mass keto acid distribution.

The studies at the Johns Hopkins GCRC were also funded by a grant from the National Institute of Arthritis, Metabolism, and Digestive Diseases and a contract under their Artificial Kidney/Chronic Uremia Program.

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Photo Feature

THESE TWIN MONKEYS
ARE A RARE PAIR

The first set of twins in the history of the Washington Primate Research Center, Seattle, was born last October. Twinning is a very unusual occurrence in monkeys (1.2 percent), and survival is even more rare. This is the first pair at the Center in over 2,200 pregnancies. The long-tailed infant macaques (Macaca fascicularis) *are both males. This type of animals is used for studies on prematurity, infancy diseases, and nutrition. The Center is supported by the National Institutes of Health Division of Research Resources. (NIH Photo #1522)*

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NEWS & FEATURES From NIH

February 10, 1976

News Feature

ASPHYXIA DURING PREGNANCY CAN CAUSE BRAIN DAMAGE

One cause of brain damage that may result in cerebral palsy or mental retardation is asphyxia during pregnancy.

The term asphyxia describes any condition when the fetus sustains an impairment in its respiratory gas exchange with the mother.

Still not fully understood by medical scientists are the severity of asphyxia required to produce injury, the basis for the wide diversity of patterns of injury induced, and the clinical circumstances which lead to asphyxia.

Ronald E. Myers, M.D., Ph.D., of the National Institute of Neurological and Communicative Disorders and Stroke, is using non-human primates in his attempts to provide an experimentally-based classification of the asphyxias. Furthermore, he hopes to describe the types of brain injury that the asphyxias produce.

Such a classification should make it possible for scientists to report their findings more precisely and to compare patterns of injury caused by the asphyxias in the animal fetus with certain kinds of brain damage in human infants.

In another study of the effects of perinatal asphyxia in monkey fetuses, Dr. Myers and other scientists are attempting to reproduce the nerve damage of human cerebral palsy and mental retardation. This goal has been partially achieved, and the investigators are continuing their search for the circumstances that lead to the brain injury produced.

The scientists are also trying to develop techniques to prevent the deterioration of the fetus when it is being asphyxiated. A main goal is to prevent or postpone the occurrence of brain injury.

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NEWS & FEATURES From NIH February 10, 1976

News Feature

PROSTAGLANDIN DEFICIENCY IN KIDNEYS MIGHT BE A CAUSE OF HYPERTENSION

The kidney is the central organ in one of the most complex body systems which has the function of maintaining a stable internal environment through removal of the end products of metabolism from the blood, and regulation of the body's electrolyte (electrical conductor) composition and fluid and acid-base balance. The kidney also affects other physiological processes, such as regulation of blood pressure and stimulation of the formation of red blood cells, according to the National Institutes of Health.

Three kidney disease groups--infectious, hypersensitive, and hypertensive --account for about three-fourths of all kidney deaths. For future reduction of this ratio, better methods of preventive treatment, intensified case-finding, and more effective prompt therapy are essential. So is the greater understanding of the basic causes and mechanisms of the diseases. The emergency measures for end-stage kidney disease, such as dialysis or transplantation, are life-saving and life-extending, but the main objective of biomedical research in this area is control and prevention.

At the State University of New York, Buffalo, James B. Lee, M.D., has found indications that a deficiency of hormone-like substances, known as prostaglandins, in the kidneys may be responsible for the development of hypertension or high blood pressure.

Dr. Lee and associates noted that prostaglandins normally present in the kidneys restored normal blood pressure when injected into hypertensive patients. The injections also brought about normal blood flow in the kidneys of the patients, as well as normal salt and water excretion. The researchers' findings support the theory that hypertension may be a deficiency disease resulting from lack of compounds that keep the blood pressure at normal levels.

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NEWS & FEATURES From NIH February 10, 1976

News Feature

CANCERLINE PROVIDES EASIER ACCESS TO CANCER INFORMATION

Cancerline (Cancer Information On-Line) is one of a number of information services developed by the International Cancer Research Data Bank (ICRDB) Program of the National Cancer Institute (NCI). In 1976 Cancerline will have more than 50,000 abstracts summarizing the results of cancer research projects that have been published in nearly 3,500 leading biomedical journals around the world since 1963.

Results of research on cancer therapy and causes make up the major portion of the Cancerline data base. However, studies of cancer epidemiology, pathogenesis, biochemistry, immunology, and other cancer biology are also included. Each year, more than 15,000 new abstracts of published cancer research results will be added to this data base.

Scientists and clinicians affiliated with approximately 450 different research centers and other organizations throughout the United States (and, increasingly, in other countries) can easily retrieve information about specific topic from Cancerline through on-line terminals linked by telephone lines to the computer system of the National Library of Medicine (NLM). Any combination of words or terms that appear in the title, text, index, or author sections of each record can be used to narrow the search to a very specific area.

The retrieved abstracts can be printed locally on a simple automatic typewriter or can be viewed on a TV-like screen. When many abstracts are retrieved, they can be printed at the NLM computer center and mailed to the researcher, usually within 24 hours. Scientists lacking easy access to a local computer terminal can usually call a search analyst in a nearly biomedical

(more)

CANCERLINE (CONT'D)

library and request a search.

In addition to abstracts of published results, a second Cancerline data base, to be made available early in 1976, has approximately 10,000 descriptions of current, on-going research projects, including nearly 1,000 summaries of research protocols for controlled clinical trials in the treatment of cancer patients.

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NEWS & FEATURES From NIH February 10, 1976

Research Illustrated

BABIES' HEARING ASSESSED BY NEW BEHAVIORAL TECHNIQUE

By JEANNETTE BELLIVEAU
University of Maryland Intern

The hearing of babies only five months old has been precisely measured using food bits and animated toys as rewards for responses to sounds, by researchers supported by the National Institute of Child Health and Human Development (see accompanying photographs).

This behavioral assessment technique, based on operant conditioning, uses a tone stimulus, presented through a headset or loudspeaker. The desired response can be either button-pushing or head-turning, reinforced either visually by a mechanical toy, or tangibly by cereal or other edible rewards. The reinforcement strengthens the child's response, which continues long enough to test his hearing threshold.

The investigators successfully measured hearing threshold levels in all infants studied between six and eighteen months of age, and in 60 percent of the five-month-olds. The results were similar to typical adult thresholds.

In the past, hearing tests were generally not precise for children under eighteen months. With careful application of operant conditioning, behavioral assessment works well with younger children and babies, and can detect hearing problems that might later impair the child's language and development.

"Two keys to this method's success," said investigator Lyle L. Lloyd, Ph.D. (NICHD), "are scaling the response expected of the child to his developmentally-determined capabilities, such as head-turning in six-month-olds, and designing a reinforcement that works because it 'turns the child on,' such as, in this case, animated toys or food."

Wesley R. Wilson, Ph.D., and John M. Moore, University of Washington Child Development and Mental Retardation Center (Seattle), T. Newell Decker, Ph.D., University of North Dakota, and Dr. Lloyd won an award for their

(more)

scientific exhibit presenting this research at the November, 1975 meeting of the American Speech and Hearing Association.

Steven is only six months old, but his hearing can be measured through careful application of operant conditioning principles. If Steven looks toward the sound, presented through a loudspeaker, a brightly-lit drumming bear rewards him. The children in this study turned their heads much more frequently when reinforced by the bear than when the sound alone was presented.

Between sounds, audiologist John Mick Moore (right) entertains Steven with toy animals. This method of hearing assessment is called Visual Reinforcement Audiometry (VRA). *(NIH Photos #1523 and 1524)*

Crystal Boyles, 12 months, thinks hearing tests are fun because she gets a cookie bit if she presses the panel while hearing a tone.

After she learns the procedure, the sound volume is gradually decreased until she no longer responds, thus indicating her hearing threshold. This method is called Tangible Reinforcement Operant Conditioning Audiometry (TROCA).

(NIH Photos #1525, 1526, and 1527)

(more)

HEARING (CONT'D)

"Oh, look at the monkey!" This time a toy monkey bangs his cymbals to reinforce Crystal's button-pushing, but otherwise this procedure is the same as TROCA. It is called Visual Reinforcement Operant Conditioning Audiometry (VROCA). *(NIH Photos #1528, 1529, and 1530)*

(more)

HEARING (CONT'D)

Kant Gumeson, 2, gets a big kick out of the weight-lifting monkey. VROCA can also be used to test the older, hard-of-hearing child.

(NIH Photos #1531, 1532, 1533, and 1534)

(All Photos provided by Jan Smyth, CDMRC Media Services)

#

NEWS & FEATURES From NIH February 10, 1976

Disease Profile

CAUSE OF PARKINSON'S DISEASE IS UNKNOWN

Parkinson's disease is one of the most severely crippling chronic disorders of the nervous system. Estimates of prevalence range from one case per 1,000 to one case per 200 population. The disease most frequently attacks people in their 50's and 60's. Parkinson's disease is rarely a primary cause of death, but it often weakens the victim so that he falls prey to other diseases, according to the National Institute of Neurological and Communicative Disorders and Stroke.

First described in 1817 by James Parkinson, a London physician, Parkinson's disease affects the brain centers involved in the control and regulation of movement. The intellect, however, is ordinarily unimpaired. Due to disordered control of movement, rigidity of the muscles develops, accompanied by uncontrollable trembling of the extremities, stooped posture, loss of facial expression, and difficulty in walking, talking, writing, or any action requiring a high degree of muscular coordination.

The cause or causes of Parkinson's disease are still unknown. Certain forms may result from a still undetected virus, and a few metallic poisons have been suspected. One theory on the cause is that coordinated muscle control depends upon a balance of two neurochemical systems, cholinergic and dopaminergic, and that the symptoms of parkinsonism arise from overactivity or underactivity of one or the other of these systems. This theory has been strengthened in the past few years by striking advances in drug treatment, which is thought to work by correcting these chemical imbalances. It tells us nothing, however, about what

(more)

causes the imbalances. Accordingly, the "big push" in research today is in finding out more about the chemistry of the brain and nervous system, and how to manipulate it for human benefit.

Treatment in the past consisted of physical therapy to help counteract the muscular rigidity, brain surgery, now used infrequently and effective mainly against tremor, and an array of drugs of very limited effectiveness.

Recent research has shown that depletion of dopamine, a natural substance found in the brain, and necessary for nerve impulse transmission, accompanies parkinsonism. A scientist at Brookhaven National Laboratory, Upton, New York, in a series of highly successful experiments in the late 1960's, found that it was possible to replace the missing dopamine by a gradual buildup of large oral doses of its metabolic precursor, an amino acid (levodihydroxyphenylalanine, abbreviated as L-Dopa, or levodopa). The treatment benefited two-thirds to three-fourths of all Parkinson patients, and as many as 20 percent were freed of all symptoms. Levodopa has thus been widely acclaimed as the first successful antiparkinsonism drug, and its discovery opened up new hope for patients and research opportunities for scientists.

The new therapy, however, has not been without problems. Chief of these has been the side effects caused by the extremely large doses necessary to control symptoms. Levodopa is broken down very rapidly in the body, and large doses are necessary to achieve the saturation required for penetration into the brain. A way around this problem has been found through the use of enzyme inhibitors, substances which slow the metabolic breakdown of levodopa, allow more time for it to penetrate,

(more)

and make possible a reduction of dosages by as much as 80 percent.

Unfortunately, even such treatment does not solve all of the patient's problems. Adventitious movements (twitching) still occur; some patients experience an "on-off" effect, in which response to the drugs is not uniform; and the drugs do not seem to slow the progression of Parkinson's disease. The drugs represent an enormous advance over the standard treatment of the 1960's, but the battle is far from won. Other drugs are being tried, and hundreds of experiments are contributing to the final answer of the molecular puzzle.

#

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See page 20

RESEARCH ADVANCES:

Method Is Devised to Measure Histamine Release from Blood.......................1
NCI Checks Chemicals that Might Be Carcinogens.......3
Scientists Apply Potential Teratogens to Animal Embryos....................6
Cold Viruses Are Not Easily Transmitted......................8
Fatty Acid Deficiency Corrected with Intravenous Fat Solution...13
Dentists' Alert: Lesions Could Be Hand, Foot, and Mouth Disease..15

NEWS AND PHOTO FEATURES:

New Technique Makes Chromosome Measurements Much More Precise..17
Methods Now Exist to Solve Many World Vision Problems......20

RESEARCH ILLUSTRATED:

NIH Holds Conference on DNA Recombination Effects..........26

DISEASE PROFILE:

Dental Research Has Enhanced Human Comfort.................31

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NEWS & FEATURES From NIH March 25, 1976

Research Advances

METHOD IS DEVISED TO MEASURE HISTAMINE RELEASE FROM BLOOD

Clinicians interested in allergy research and patients with allergic symptoms could profit from a method devised to measure the release of histamine from small amounts of whole blood. Histamine is a substance that induces many shock and allergic reactions.

On March 10, 1976, Dr. Reuben P. Siraganian, Acting Clinical Director of the National Institute of Dental Research, told the members of the American Academy of Allergy meeting at the Americana Hotel, San Juan, that his rapid, automated procedure is so sensitive that it can detect fluorimetrically as little as half a nanogram (nano = a billionth) of histamine in blood. Compared to the current method of assaying histamine released from washed white blood cells, Dr. Siraganian's equipemtn is 10 times more sensitive, completely automated and can analyze 30 samples an hour.

The new assay correlates well with skin tests and clinical observations, Dr. Siraganian reports. He thinks it could be substituted for them whenever highly sensitive patients might suffer anaphylactic shock if skin tested. He has compared this method with skin tests and also with the washed leukocyte assay in a group of 82 individuals.

He tested three concentrations of nine commercial allergens. These were separate mixtures of: pollens of grasses, trees, ragweeds, and other weeds; several kinds of feathers and of molds; cat and dog danders; and house dust. Heparin was added to the blood to prevent clotting, then .5 ml of the blood sample was put in a test tube with the chosen concentration of

(more)

HISTAMINE (CONT'D)

allergen and allowed to interact for an hour at 37°C. Thereafter the blood was centrifuged to separate the heavier cells and solids from the serum which contained the histamine released from the leukocytes. Finally, special automated equipment was used to measure the amount of histamine.

Dr. Siraganian does not think that his method will completely eliminate the need for skin tests. But he hopes that it will serve to screen patients rapidly, safely, and inexpensively against the common allergens. Moreover, because it is quantitative, it could be a valuable research tool. Dentists suspect that certain troublesome conditions such as canker sores and Sjogren's syndrome may have an allergic or autoimmune origin.

The percentage of false positive responses in this study was small (0.2 percent), and the concordance with clinical observations, skin tests, and the washed leukocyte test was high--about 89 percent between skin tests and this method for those individuals with strong allergies. Hence, Dr. Siraganian believes that his test will identify most persons clearly allergic to a given substance. Those who give weak reactions to skin tests tend to appear negative by this automated test. Dr. Siraganian notes that there are always some patients whose leukocytes fail to release histamine in any test tube assay although skin tests show that they are allergic. Leukocytes in about 11 percent of his subjects act this way.

#

Research Advances

NCI CHECKS CHEMICALS THAT MIGHT BE CARCINOGENS

A growing number of compounds, of widely differing structure and chemical characteristics, have been identified as carcinogens--cancer-causing agents--in tests with animals. Only about 30 chemicals have been associated clearly with cancer causation in man, but chemical carcinogens have become suspect as occurring more widely in the environment than previously believed.

Cancer might be prevented by eliminating human exposures to carcinogens wherever possible. In addition, however, scientists have been seeking ways to block the action of carcinogens or reverse the cancer-inducing process at an early stage of cell transformation. This alternative approach has received encouragement in recent years from evidence that many different chemical carcinogens may act at the molecular level through similar mechanisms. Research on an effective counteracting agent thus might lead to prevention of cancer caused by a broad range of carcinogens.

Scientists in several laboratories have been exploring the carcinogenesis-inhibiting properties of compounds that act as antioxidants. Antioxidants block chemical reactions of substances with oxygen and are used to prevent deterioration of foods, rubber and other materials. Lee W. Wattenberg, M.D., a National Cancer Institute grantee at the University of Minnesota Medical School, Minneapolis, has reported in the *Journal of the National Cancer Institute*, August 1975, that antioxidants significantly decrease cancer formation in mice and rats when administered either before or with chemical cancer-causing agents.

Dr. Wattenberg found cancer inhibition with three widely used antioxidants:

(more)

butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), and ethoxyquin. More recently, he has extended his findings to antioxidants that are sulfur-containing compounds with molecular structures different from the earlier compounds.

Past studies have shown that the carcinogen 7,12-dimethylbenz(a)-anthracene (DMBA) caused mammary (breast) cancers when given by oral administration to female rats. Another carcinogen, benzo(a)pyrene (BP), caused a high incidence of cancers of the forestomach when included in the diet of mice. When Dr. Wattenberg added one of the sulfur-containing antioxidants--disulfiram or dimethylthiocarbamate--to the diet of rats given DMBA, he observed a decrease in the number of rats with cancer and the number of tumors per animal. An additional sulfur-containing compound, benzyl thiocyanate, had a similar effect. Disulfiram also inhibited stomach cancer formation in mice given BP. The other two compounds were not tested in mice.

The Minnesota scientist fed the inhibitors to randomized groups of six-week-old female Sprague-Dawley rats and gave the animals DMBA by oral incubation one week after starting the experimental diets. Sixteen weeks later, 22 percent of the rats fed disulfiram and 33 percent of the rats fed dimethyldithiocarbamate had developed mammary cancers, compared with development of tumors in 61 percent of a control group given no antioxidant. In a second experiment, rats fed benzyl thiocyanate had a tumor rate of eight percent while a control group tested at the same time developed tumors in 79 percent of the animals.

In a test procedure with the Ha/ICR strain of female mice fed a diet containing BP, no cancers of the forestomach developed in animals given a diet containing disulfiram in addition to the BP. Tumors developed in 40 per-

(more)

cent of the animals fed BP without the antioxidant.

All antioxidants do not protect against every type of chemical carcinogen. Thus whereas BHA inhibits pulmonary adenoma formation resulting from administration of BP to mice, the sulfur-containing antioxidants are ineffective in this situation.

Dr. Wattenberg's research has broadened the range of antioxidant compounds found to inhibit chemical carcinogenesis in experimental systems. The data suggest that different chemicals with a common function can act to interfere with cancer causation. The results are consistent with the hypothesis that many carcinogens may act with mechanisms that have common features.

Dr. Wattenberg noted that his research does not reveal the mechanism by which the sulfur-containing compounds prevent the initiation of tumors. One possibility is that the antioxidants are effective because of their antioxidant properties. Many carcinogens undergo metabolic changes in the organism with the production of highly reactive compounds. These highly reactive derivatives are the actual chemicals causing the malignant alterations in cells. The antioxidants could function by reacting with these cancer producing derivatives thus protecting the tissues from harmful effects.

A second type of possible mechanism of inhibition by the sulfur-containing compounds is indirect. In this instance, the inhibition would be produced by an action such as altering enzyme activity. Determination of the mechanism of inhibition of cancer-producing chemicals by antioxidants is of considerable importance in order to identify compounds that have inhibiting potential and also to devise inhibitors with optimal properties. Studies of this nature are continuing in Dr. Wattenberg's laboratory and elsewhere.

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Research Advances

SCIENTISTS APPLY POTENTIAL TERATOGENS TO ANIMAL EMBRYOS

There are probably no health-related disorders quite as tragic as those resulting in malformed babies. To help prevent these tragedies, National Institute of Environmental Health Sciences researchers are developing models to study the ways birth defects are produced, and are seeking animal models to rapidly predict human teratogens (defect-causing agents). These models include mouse, rat, and rabbit embryos and mouse cell, tissue, and organ culture systems.

Robert E. Staples, Ph.D., and Ralph R. Maurer, Ph.D., apply test agents directly to mouse, rat, and rabbit embryos to detect potential teratogens. Direct exposure circumvents compound changes in the pregnant animal, and permits more accurate determination of the amount of test compounds to which the embryo was exposed.

Embryos are taken from donor animals and then exposed to various chemicals or conditions during culture. Following exposure, some of the embryos are re-implanted into the uterus of females ; others are examined for structural or chemical changes. The re-implanted embryos are examined for defects. Results are compared to those seen following administration of the test agent to the dam.

This procedure is being validated with well-studied chemicals such as thalidomide, a drug which resulted in hundreds of babies with malformed limbs born to women who took it while pregnant as a tranquilizer. Accumulated data indicate that high thalidomide doses are lethal to embryos in later stages of development, but do not affect formation or development of blastocysts (an earlier stage). Structural malformations have not resulted from direct

(more)

TERATOGENS (CONT'D)

application of thalidomide or additional teratogens to the embryo.

Viable mouse tissue and organ culture systems are being developed by Dr. Judson W. Spalding and his coworkers to investigate how chemical agents affect the development of reproduction cells. These cells, if found defective, often result in sterile offspring, or offspring with a wide range of inborn genetic errors.

Various environmental agents and drugs are known to affect reproduction and development, but their specific molecular effects on reproduction cells (oocytes and spermatocytes) during the early stages of development are not well understood. In the ovary organ systems, Dr. Spalding has shown that oocyte maturation occurs in a manner analogous to oocyte maturation in the whole animal (*in vivo*) occurring about 25 days postconception. The scientists' continuing work is aimed at obtaining consistent and reproducible stages of growth and maturation. When this model is fully developed, effects of chemicals on embryonic and postnatal germ cell differentiation may be compared with effects on the development of the male and female sex cells (gametes) and fertility in the whole animal. Then a rapid *in vitro* test system will be available that can be used to predict *in vivo* teratogenicity.

#

Research Advances

COLD VIRUSES ARE NOT EASILY TRANSMITTED

In spite of popular impressions, cold viruses are not easily transmitted from one person to another, according to University of Wisconsin scientists. This resistance to virus transmission has led the scientists to suggest that a simple device, such as facial tissue treated with a virus-killing substance, may help break the chain of rhinovirus (cold-causing virus) transmission.

In their study of person-to-person transmission of rhinoviruses (the first of its type), Elliot C. Dick, Ph.D., and his associates found that the major factors involved were severity of the cold sufferer's sumptoms, amount of time spent with the ill person, and amount of virus shed.

Virus shedding is measured by washing the nasal chanbers with a solution, which is then examined to determine how much virus is pouring out of nasal cells into the surrounding fluids. Although it sounds like an uncomfortable procedure, Dr. Dick says that nasal washing actually "makes the person feel better."

Prior research on the common cold has most often focused on the natural spread of the infection through families or neighborhoods. Dr. Dick's study of 24 maried couples used laboratory-grown rhinovirus to inoculate one partner of a cold-free couple. This enabled control of rhinovirus serotype, and measurement of symptoms, virus shedding, and type and amount of contact.

Twelve volunteers (donors) were inoculated intranasally with rhinovirus serotype 16, of which five (41 percent) transmitted the virus to their spouses. All five transmitters spent at least 122 hours with their spouses during the observation week, while six of the seven non-transmitters spent less than

(more)

COLDS (CONT'D)

122 hours at home.

Twelve other donors received rhinovirus serotype 55. Four of these 33 percent transmitted the virus to their spouses and, again, ability to transmit was related to amount of time spent together at home during the week. The overall rate of transmission was only 38 percent.

The investigators also found a strong correlation between virus shedding (usually accompanied by severe symptoms) and ability of the donor to transmit the virus. Presence of virus on the hands and around the nostrils of a donor also related positively to transmission.

Eight of the 13 donors who reported either severe or moderate cold symptoms transmitted their virus, whereas only one of the 11 donors with mild or no symptoms transmitted virus.

Most donors had the most severe symptoms and shed the most virus on the second and third days after inoculation; and the most common interval between inoculation of the donor and recovery of the virus from the spouse was five days. If one allows a day for incubation of the virus in the donor and another for incubation in the recipient, it is clear that virus transmission probably took place on days two to three, during the peak period of virus shedding.

The scientists did not understand why persons with mild colds were unable to transmit their infection to their spouses, even with many hours of contact, since only minute amounts of lab-grown virus had been required to infect the donors. But whatever the reason for resistance, the scientists feel that it is encouraging from a preventive standpoint.

(more)

COLDS (CONT'D)

Results of this study are of particular significance in families with asthmatic children. In a recent National Institute of Allergy and Infectious Diseases supported investigation conducted by Dr. Dick and Dr. Charles Reed, University of Wisconsin Asthma and Allergic Disease Center, it was found that rhinovirus infections were the principal causes of asthmatic attacks in allergic children.

This work was reported in the January issue of the *Journal of Infectious Diseases* by Dr. Dick and Donn J. D'Alessio, M.D., Judy A. Peterson, and Claire R. Dick. Partial research support also was received from the National Aeronautics and Space Administration, which is concerned with the transmission of colds in persons prior to and during space flight.

(more)

Elliott C. Dick, Ph.D., Professor of Medicine, and microbiologist Patricia Boehme inspect some incubating rhinovirus 16. (NIH Photo #1535)

(more)

Dr. Dick examines the growth of virus in a cell culture. (NIH Photo #1536)

#

Research Advances

FATTY ACID DEFICIENCY CORRECTED WITH INTRAVENOUS FAT SOLUTION

A Seattle grantee of the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD) has used an intravenous fat solution to correct essential fatty acid deficiency associated with skin lesions in three patients receiving total parenteral nutrition. It is suggested that parenteral fat preparations should be made available for such patients.

In the past, essential fatty acid deficiency, which has been delineated only in experimental animals and in infants maintained on fat-free intravenous feeding, has been considered a rare entity. In the last two years, with increasing use of total parenteral nutrition for prolonged periods of time, however, several investigators have reported essential fatty acid deficiency in adults undergoing such therapy.

The present research details essential fatty acid deficiency associated with progressive skin lesions in three patients undergoing prolonged total parenteral nutrition, and correction of these abnormalities with an intravenous fat emulsion. Thus, current evidence indicates that essential fatty acid deficiency is an increasingly common clinical problem in such a setting, and that the existing FDA restrictions on the use of intravenous fat should be modified to permit its administration in special circumstances.

Three patients (ages 60, 53 and 13) undergoing fat-free parenteral alimentation at home developed skin lesions, characterized by dryness and scaly appearance, 46 days, six months, and two years, respectively, after initiation of such therapy. The lesions, initially confined to skin fold areas but subsequently becoming generalized, were associated with a markedly abnormal plasma lipid pattern. The patients were given 500 ml/day of intravenous fat

(more)

FATTY ACIDS (CONT'D)

in the form of linoleic acid (Intralipid-Cutter Laboratories).

All three patients showed improvement at the end of the first week of intravenous fat alimentation. Serial measurements of plasma fatty acids showed a progressive normalization of the abnormal pattern, accompanied by a dramatic improvement in the skin lesions. The skin cleared completely in two older patients within two and four weeks, respectively, while only signs of urticaria pigmentosa were present in the 13-year-old after six weeks of fat therapy.

Thus, it would appear that essential fatty acid deficiency might occur in all patients receiving long-term total parenteral nutrition. With the information now available its prevention, through inclusion of intravenous fat preparations in any program of long-term parenteral nutrition, becomes a clinical imperative.

NIAMDD grantee Dr. Belding H. Scribner and associates of the University of Washington, Seattle, reported their findings in the *Annals of Internal Medicine*, November 1975.

#

Research Advances

DENTISTS' ALERT: LESIONS COULD BE HAND, FOOT AND MOUTH DISEASE

National Institute of Dental Research grantee, Ralph V. McKinney, D.D.S., Ph.D., of the Medical College of Georgia, alerts dentists to hand, foot, and mouth disease, a contagious, yet self-limiting condition. Noting that dentists may be the first to see oral lesions, which are early signs of the disease, Dr. McKinney warns that a dentist may contract it or may carry it without symptoms to patients and to members of the family.

Hand, foot, and mouth disease usually clears up spontaneously in two to three weeks. Treatments available are merely palliative.

The disease can be mild with vesicular (blister-like) or ulcerative lesions as the only symptom, or it can be painful, making eating, talking, and walking difficult. Sometimes, it begins with a sore mouth, fever and general malaise. About two days later, the oral blisters appear, followed by blisters on the hands and feet. Young children also may develop them on the buttocks and back of the thighs.

Both dentists and patients should be aware of the disease because it is easily transmitted from person to person. Dentists should be especially careful not to touch suspicious lesions and to learn to distinguish lesions of this disease from those of herpes and other infections which are similar in appearance. However, the diagnosis of hand, foot, and mouth disease can be confirmed only when the virus, *Coxsackievirus group A, type 16*, is isolated in suspensions of mouse cells taken from animals infected with blood or stool specimens from patients with the disease.

A case report discussed in the July 1975 issue of the *Journal of the*

(more)

LESIONS (CONT'D)

American Dental Association illustrates the contagious nature of the disease. The four-year-old daughter of a dentist complained about a sore spot on her tongue. Three days later, when the two-year-old pointed to an extremely sore mouth, the father noted vesicular eruptions on the roof and sides of the mouth. In addition, the young girl had a mild fever, runny nose, and general malaise. About one day later, the four-year-old had vesicular lesions along the soles of her feet and toes. These lesions were so painful that walking was difficult. Although neither the child's mother nor her seven-year-old sibling developed lesions, blood test showed they had contracted the disease. The seven-year-old did have elevated temperature. Approximately two weeks later, when the children's lesions had healed, the father developed several vesicular lesions on his hands. He showed no other signs.

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NEWS & FEATURES From NIH

March 25, 1976

Photo Feature

NEW TECHNIQUE MAKES CHROMOSOME MEASUREMENTS MUCH MORE PRECISE

A new technique for making unprecedentedly precise chromosome measurements has reached the point of initial clinical applications, promising a substantial improvement in the accuracy of information available to physicians analyzing pregnancies and genetic diseases.

In addition, in ongoing studies, the technique is beginning to provide substantial, quantitative information on population genetics -- for example, on the existence of "normal," non-pathological chromosome variations and their heritability.

The technique involves measuring the amount of DNA (genetic material) in each chromosome. It is based on an instrument known as CYDAC (Cytophotometric Data Converter), which combines a visible light microscope, special scanning electronics and automated image processing. CYDAC has been developed over the past 12 years, initially at the University of Pennsylvania and since 1973 at the Lawrence Livermore Laboratory (LLL).

Development has been supported by the National Institute of General Medical Sciences and the U.S. Energy Research and Development Administration. LLL is operated for ERDA by the University of California. Leader of the present CYDAC development and application effort is Dr. Brian Mayall.

In a joint study, a University of California at San Francisco physician recently used data provided by LLL in a prenatal diagnosis for a possible birth defect. The physician had provided the Laboratory with cells obtained from an amniocentesis, or uterine tap. The physician suspected a #18 chromosome abnormality associated with extreme mental retardation as well as physical deformation.

(more)

MEASUREMENTS (CONT'D)

The abnormality is too subtle to be detected unambiguously by conventional means. It is the absence of at least five femtograms (millionths of a billionth of a gram) of DNA from a chromosome that should have 140 femtograms.

The CYDAC analysis found that the chromosome aberration was not present. Based on this information, the physician advised his patient against termination of pregnancy. (At full-term, a healthy baby was born.)

"The ability to provide clinical information using CYDAC is extremely gratifying, and results from widespread advances in biological understanding of cytogenetics, in computations techniques and in electronics," said Dr. Mayall.

"Years ago, when we began this project at the University of Pennsylvania, it was not at all clear that we were getting into anything but basic research. Our techniques were too cumbersome and slow for clinical application. There is still no likelihood of replacing conventional cytogenetic analyses, but we can complement them and provide quantitative data that cannot now be obtained any other way."

In population genetics, LLL researchers have been able to determine whether a chromosome comes from an offspring's mother or father on the basis of precise DNA measurement, with greater than 90 percent probability. Such determinations have been made previously on the basis of occasional, inherited variations in a chromosome's shape or size, but the DNA measurement provides a significantly more consistent tool for this purpose.

The ability to trace chromosome maternity or paternity creates a mechanism for studying the means by which associated genetic characteristics may be inherited. In addition, when variations in chromosomes are determined to be new, not inherited, researchers can explore possible causes for the variations. They are studying one such case now in which a son's anomalous chromosome (#19) is not traceable to either parent.

#

MEASUREMENTS (Cont'd)

This is Dr. Brian Mayall of ERDA's Lawrence Livermore Laboratory at CYDAC, which provides unprecedently-precise measurements of chromosome DNA content, with both basic and clinical implications. (NIH Photo #1537)

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March 25, 1976

Photo Feature

METHODS NOW EXIST TO SOLVE MANY WORLD VISION PROBLEMS

If known methods of care, diagnosis, and treatment were used worldwide, two-thirds of all blindness could be prevented and at least 20 percent of existing blindness could now be corrected, according to the World Health Organization (WHO) and NIH's National Eye Institute.

WHO also predicts that the number of blind persons in the world will double to approximately 30 million by the end of this century, unless decisive action is taken to implement these known prevention and treatment methods.

In an effort to forestall the needless human suffering and economic loss this dire prediction portends, WHO is directing world attention to the urgent global health problem of preventable blindness on World Health Day, April 7.

"Foresight Prevents Blindness," the theme of this year's annual observance, dramatizes both the need and the utility of timely preventive measures to alleviate eye disorders which lead to blindness.

Six major disorders account for 80 percent of all blindness. Three are common in every country of the world--glaucoma, cataract, and eye injury. The other three are widespread in the developing world--trachoma, onchocerciasis, and xerophthalmia. The latter three primarily affect the cornea and are the chief causes worldwide of blindness in children.

None of these disorders, which together are responsible for the present sightlessness of at least 10 million people, need result in blindness.

Serious visual loss from glaucoma can be avoided by early detection and prompt medical treatment. The medication, usually in the form of eyedrops, normally can control the increased pressure within the eye which may permanently damage the optic nerve.

(more)

VISION (CONT'D)

Cataract, which cannot be prevented, can be corrected through highly successful surgery to remove the clouded lens.

Ocular injuries to an estimated 260,000 persons annually in the United States alone can be minimized by prompt medical care and sensible safety precautions on the job, at home, and during recreation.

Antibiotics and in some cases surgery can prevent or correct blindness from corneal diseases such as trachoma (a contagious, infectious disease associated with overcrowding, lack of water, and inadequate sanitary conditions). Eradication of the disease-carrying blackfly can prevent onchocerciasis or "river blindness," a parasitic disease transmitted by the blackfly. Vitamins and other dietary supplements may help protect the vision of children against xerophthalmia, a corneal disease associated with malnutrition.

In the United States and other developed countries, readily available medical care has helped to reduce the toll of preventable blindness. But despite improved diagnostic and treatment procedures, approximately 7,000 Americans will become legally blind this year from glaucoma and an additional 8,500 people from cataract.

Many glaucoma victims are not aware they have this usually painless eye disease until a substantial amount of vision is already lost. And many cataract patients refuse surgery from fear or for economic or social reasons.

In the developing world, these same obstacles to treatment may be magnified by poor nutrition and inadequate sanitation as well as by the shortage of medical personnel, supplies, and facilities.

In an effort to overcome these problems, the World Health Organization assists its member nations in their prevention and treatment programs. Treatment programs in some countries are provided by eye care medical caravans

(more)

which travel to remote areas and set up camp in tents, huts, schools, or temples. International medical teams together with local medical personnel may perform as many as 30 to 40 cataract operations daily in addition to treating other eye disorders.

WHO trachoma control projects include public education programs on hygiene and distribution of antibiotic ointments as preventive measures against this highly communicable disease and the ocular complications it causes. Trachoma affects an estimated half-billion people and causes blindness and severe visual disability in from five to 10 million individuals, primarily in the developing world. It is also found, however, in some areas of nearly every country, including part of the United States.

One of the most important WHO programs is control of "river blindness," or onchocerciasis, for which there are no drugs suitable for mass treatment programs. The project emphasizes control of the *(Simulium)* blackfly through large-scale insecticide spraying of breeding sites and also includes research into entomological and environmental factors. In the countries affected, health personnel at all levels are being trained in control methods and in basic health services.

WHO has assisted several countries in implementing programs for the detection, treatment, and prevention of xerophthalmia in addition to providing massive supplies of vitamins.

Another international organization, dedicated to preventing blindness, is collaborating with WHO in projects to assist developing nations. The newly-formed International Agency for the Prevention of Blindness (IAPB) is undertaking a worldwide effort to mobilize resources for implementing prevention

(more)

VISION (CONT'D)

and treatment programs.

The IAPB's Priorities and Projects Committee, composed of international experts on the six leading causes of blindness, recently met to formulate specific programs for implementation in some developing countries.

The Committee is chaired by Carl Kupfer, M.D., Director of the National Eye Institute which, along with the Fogarty International Center, hosted the conference at the National Institutes of Health. The projects considered for implementation included public education, delivery of eye care, utilization of allied health personnel, research, and combinations of these activities.

Chapters of the IAPB already are active in 33 counties and others are being formed in 17 additional countries. The U.S. National Committee is headed by Mrs. Virginia Boyce, Executive Director of the National Society for the Prevention of Blindness, Inc. (NSPB).

To highlight World Health Day and known ways to prevent blindness, the National Society for the Prevention of Blindness will conduct glaucoma screening among United Nations delegates and will also test the vision of diplomats' children at the United Nations International School on that day.

Similarly, local NSPB chapters across the country will conduct community-wide vision and glaucoma screening tests to mark World Health Day.

President Ford, in a traditional World Health Day message, commended the World Health Organization for its work in protecting the health of all people and for calling attention to the urgency of reducing preventable blindness.

(more)

VISION (Cont'd)

Eye examinations are conducted at a health center (left photo) in Latin America. In the right photo, a home visit is made by a health worker who will administer Vitamin A to all children under four. Xerophthalmia, an eye disease caused by lack of Vitamin A, can lead to blindness. (NIH Photos #1538 and 1539) In the cover photo, school children are taught to treat one another so that treatment can be continued after the departure of the trachoma control team.

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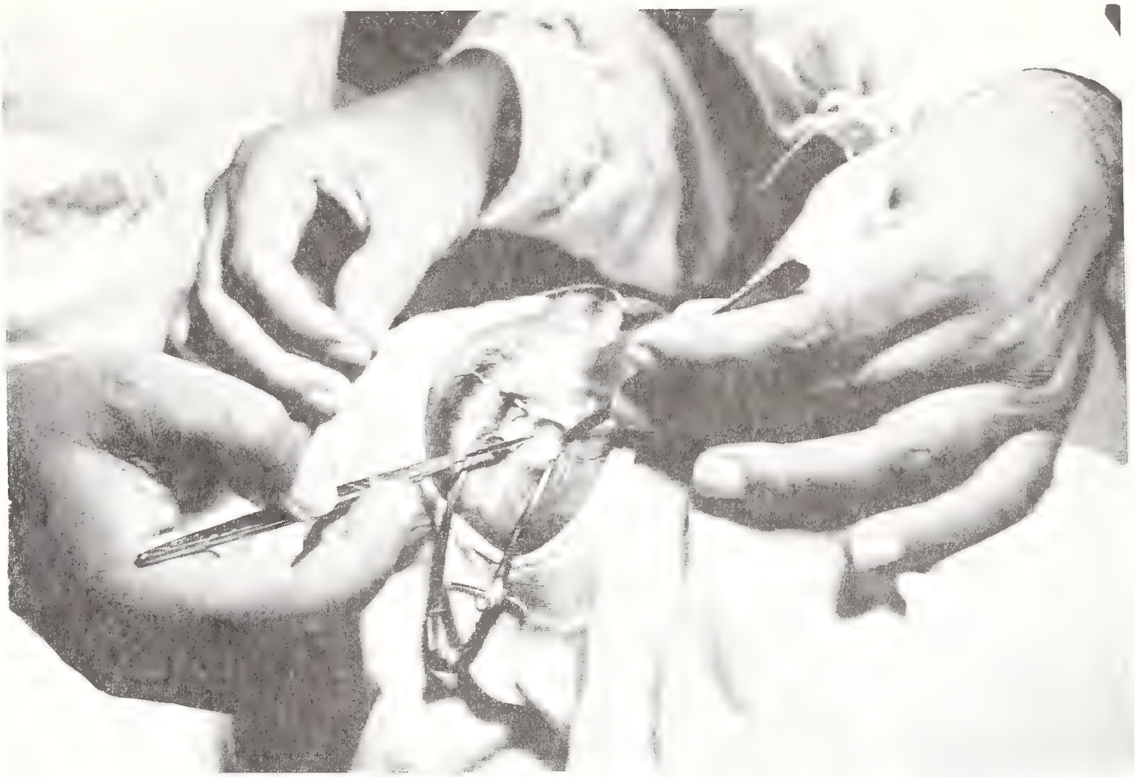

Sight loss because of cataract can be restored by a simple and relatively-low cost operation. Cataract operations are being carried out (top photo) at a temporary "eye camp." The camp (bottom photo) can serve many residents of a community. (NIH Photos #1540 and 1541)

#

NEWS & FEATURES From NIH

March 25, 1976

Research Illustrated

NIH HOLDS CONFERENCE ON DNA RECOMBINATION EFFECTS

A conference on the potential effects of experiments on DNA recombination was held on February 9-10 at the National Institutes of Health.

A controversial issue in genetics, DNA recombination has potential in several areas of human concern, including medicine, agriculture, energy, and ecology.

The Advisory Committee to the Director, NIH, and other participants were asked to consider proposed guidelines and requirements for NIH support of recombinant DNA research.

Attended by the general public and news media, proposed guidelines considered at the conference were evolved from the deliberations of three scientific conferences over an 18-month period beginning with the moratorium on all DNA recombinant research voluntarily imposed by U.S. scientists in July 1974.

The first meeting was held at Asilomar, Pacific Grove, California, in February 1975. The recommendations of the Asilomar conference were studied during a July 8, 1975 meeting at Woods Hole, Massachusetts, where a second version of the guidelines was drafted; and a third draft was produced December 4-5, 1975 in La Jolla, California.

Those facts and opinions presented at the meeting will assist the NIH Director and his advisors in an attempt to finalize specific guidelines for experiments with DNA recombinants aimed at assuring safe and beneficial results.

The Director, NIH, will hold a two-day meeting with the DNA recombinant working staff, April 1-2, to consider various questions that, in the Director's view, need further clarification.

(more)

DNA (Cont'd)

This is an example of laboratory procedure being carried out under "P-2" or "P-3" containment conditions. Researcher is seen at a partial barrier cabinet with an open front, commonly used for low to moderate-hazard manipulations. Cabinet is constructed of stainless steel and glass. Negative air pressure is maintained over the work surface, ensuring that air flow is inward toward research material--not away from it. This safety measure restricts spread of any vapors or micro-organisms. Under "P-1" conditions, the procedure could be conducted on the open bench. (NIH [illegible])

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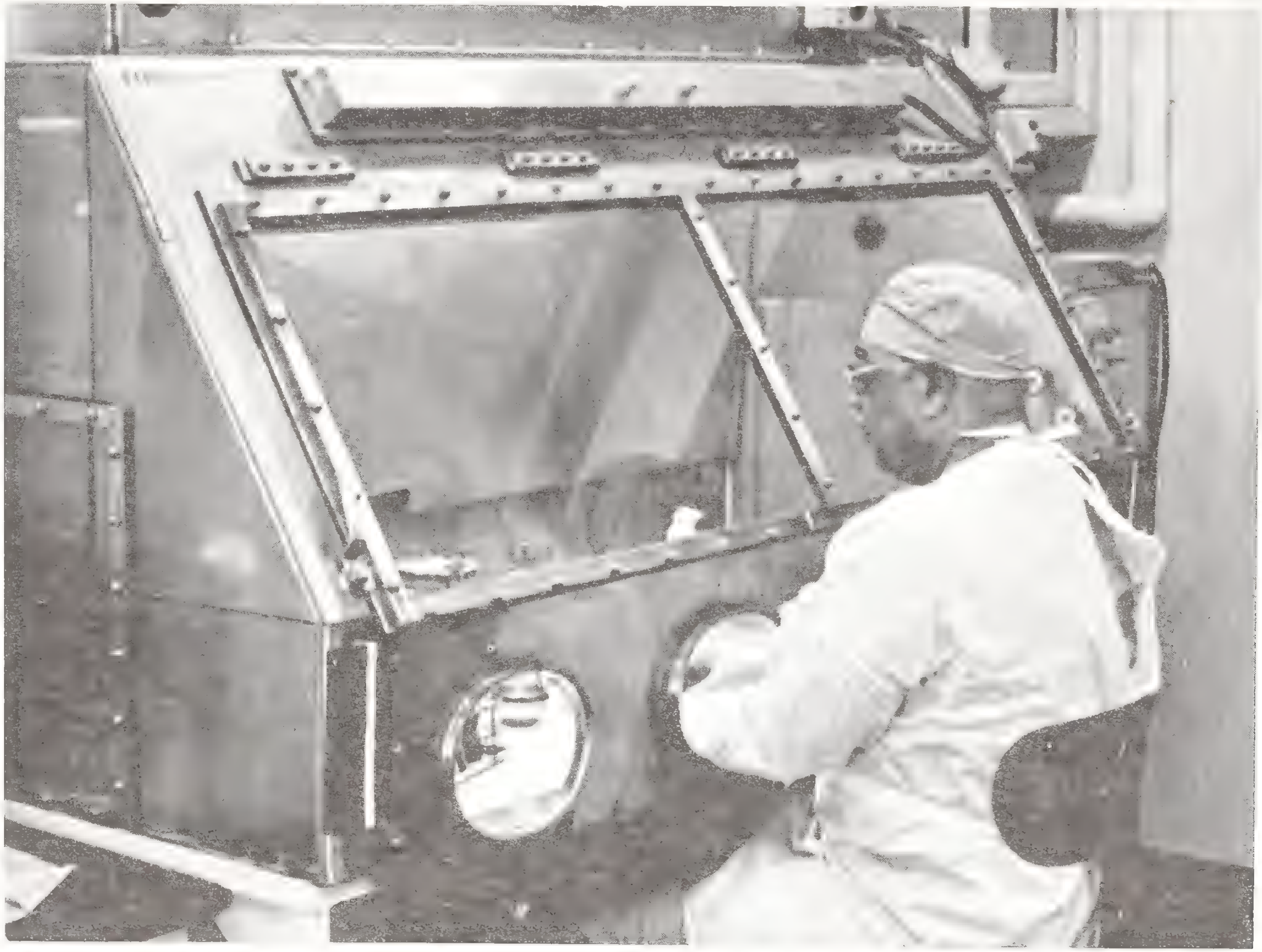
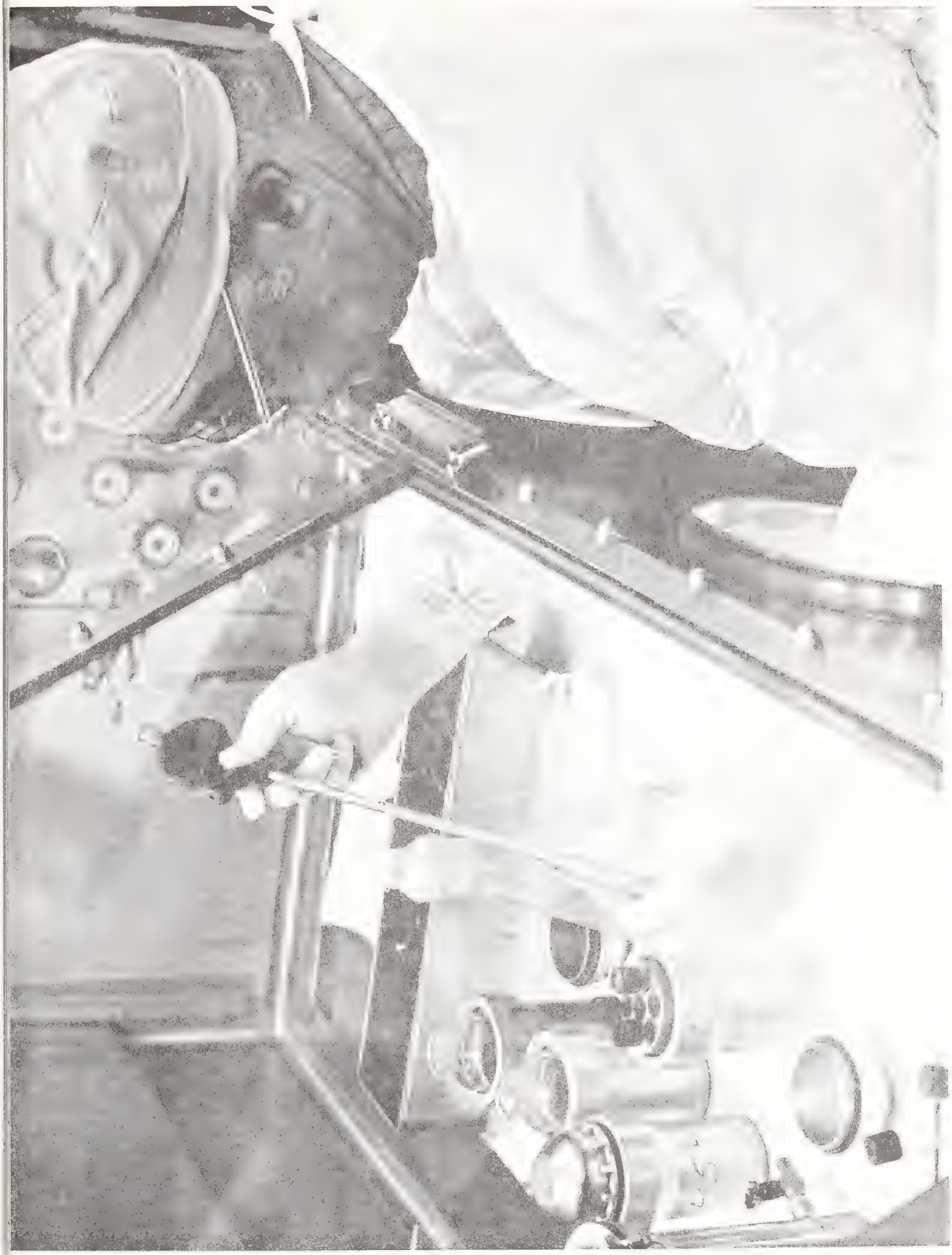
DNA (Cont'd)



This is an example of a biological safety cabinet used for "P-3" containment. Glove panels without the gloves attached are fitted on the front of the isolation cabinet. This increases the rate of air flow and reduces any spilling or spattering that may occur as materials are handled in the cabinet. The cabinet uses a high-efficiency microbial filter for air leaving the unit. The air is ducted to the nearest exhaust manifold. (NIH Photo #1543)

(more)

DNA (Cont'd)



This is a view of a work surface as it would appear under "P-3" containment conditions. Note rubber gloves enclosing cuffs of researcher's protective clothing. Biological safety cabinets used at the various containment levels are decontaminated with steam and formaldehyde. (NIH Photo #1544)

(more)

A simulation of laboratory procedures under "P-3" and "P-4" containment conditions is shown here. Tightly-sealed isolation cabinets, made of stainless steel and glass, are used to prevent contact with bacteria. Rubber gloves are attached to the cabinets. Equipment, materials and animals are passed in through devices that prevent the escape of bacteria. Nothing is removed from the cabinets until all bacteria have been destroyed by filtering and burning exhaust air drawn from the cabinets. Any waste produced is sterilized by heating it to temperature levels that will kill the most resistant micro-organism known. (NIH Photo #1545)

#

NEWS & FEATURES From NIH March 25, 1976

Disease Profile

DENTAL RESEARCH HAS ENHANCED HUMAN COMFORT

If George Washington were alive today, regardless of how he might view the trying political questions and actions of the past 200 years, he would certainly applaud the progress in human comfort provided by the dental sciences.

The possessor of the most famous set of false teeth in American history would be understandably amazed at the ease and painless procedures of tooth extraction, in comparison with the more primitive methods in vogue in his day. Quite possibly he would be impressed with the wide use of the toothbrush, toothpaste, and dental floss in personal oral hygiene programs that help prevent decay, periodontal disease, and tooth loss.

A cause for even greater astonishment might be community water fluoridation, whereby the simple act of drinking water daily would contribute to caries (tooth decay) prevention. By 1945, forerunners of the National Institute of Dental Research (created three years later in Bethesda, Maryland, as one of the National Institutes of Health) had established the scientific base for water fluoridation as an effective caries-preventive procedure. Later studies were to show that daily intake of water containing one part per million of the fluoride ion reduces the incidence of tooth decay by 50 to 60 percent.

Unfortunately, President Washington did not have the benefit of community water fluoridation and modern knowledge to help preserve his teeth. Nor were improved restorations available to spare him the description of "the hero with the ill-fitting teeth."

By the time of his inauguration in 1789, he had only one natural tooth

(more)

left, which presumably served as an anchor for the lower denture. Eventually, it loosened and came out.

Contrary to folklore, Washington's dentures were not made of wood, nor were they fashioned by Paul Revere. It is believed that five different types of teeth were used, including tusks from elephants, hippopotamuses, cattle, and probably a walrus, as well as some of his own.

None of the various dental fixtures used to restore the President's teeth could have been comfortable or efficient. In addition, his speech must have been adversely influenced. Long words and the sibilant "s," still a problem for many persons today, undoubtedly harassed him as well as those listening to him.

Today, even if he had lost all of his teeth, the plight of some 23 million Americans at present, the finest dental and restorative procedures could give him comfortable chewing service and improved facial contours. He could enjoy life much more, could laugh more easily and frequently, and he might find that his appearance was more presentable. He could select more varied foods and eat them without embarrassment even at official functions.

In the early days of this country, most dentists practiced outdoors and extractions were the most common treatment. In addition to those who set up offices at village fairs, the blacksmiths of the time enjoyed a profitable sideline in dentistry. Later individual dentists made much of their equipment and dentures in dark back rooms. It was about 1900 that the need for sterility made its impact on dentistry. Dentists changed from street dress, or even formal attire, to special clinician jackets.

(more)

DENTISTRY (CONT'D)

Since Dr. John Greenwood fashioned false teeth for our first President, the practice of dentistry has been revolutionized. Notable changes include more scientific approaches to diagnosis and treatment resulting from expanded knowledge about dental diseases, improved anesthetics and procedures, improved materials and equipment, and the introduction of more efficient dentistry with auxiliaries, such as the hygienist and dental assistant working with the dentist as a team.

Dental research has been a key force in improving the dental health of the Nation and holds promise for even greater progress in the future. In addition to its role in community water fluoridation, the National Institute of Dental Research has:

* Developed laboratory evidence that tooth decay is a transmissible disease caused by specific microorganisms;

* Shown that both what is consumed (notably sugar) and the frequency of eating have a marked effect on the occurrence and severity of caries.

* Demonstrated how clinging bacterial films called plaque contribute to both caries and periodontal disease, pointing to possible control of these diseases through antibiotics, vaccines, and other approaches;

* Developed evidence that inflammation leading to tissue damage in one type of periodontal disease is sometimes a local overreaction to bacterial products;

* Increased the effectiveness and safety of high-speed drills by providing information and guidelines on the best cutting speeds and the proper use of coolants;

* Contributed significantly to improvement and refinements of methods

(more)

of general anesthesia for ambulatory patients by identifying, for the first time, the full range of physiological responses to a variety of general anesthetic agents.

* Provided the research basis for several composite materials for filling teeth and for sealing pits and fissures in chewing surfaces of molars, and developed new alloys having greater strength, lighter weight, and less corrosiveness than compounds commonly used for restorations; and

* Made advances in the area of materials for artificial tooth implants as well as increasing knowledge about the body's reactions to transplants.

Turning from the extensive contributions of the dental sciences and dental technology, there is yet another outstanding advance in dentistry since the days of George Washington. A most significant development is the increased public awareness of the need for dental care and its availability, as well as the importance of practicing preventive dentistry in the home.

#

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NEWS&FEATURES FROM NIH

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April 25, 1976

See page 16

RESEARCH ADVANCES:

Polymerized Ragweed Antigen E May Help Sufferers of Hayfever 1
NIAID Team May Have Grown RVL Agent in Tissue Culture 3
Biofeedback Training Can Ease Severe Facial Pain 5
Scientists Study Treatment of Periodontal Disease 7
Special Transfusions Are Tried to Aid AML Patients 9

NEWS AND PHOTO FEATURES:

Treatment Is Developed for Rapid Periodontitis 12
Researchers Seek Safer Antivenin 16
MRFIT Promises to Be Important Heart Study 19
Possible Link Seen Between Diabetes and Thyrotoxicosis 22
NIH Schedules Public Open House May 1-2 24
DHEW Proposes New Peer Review Rules 26

RESEARCH ILLUSTRATED:

NLM Presents Special Bicentennial Exhibit 27

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Research Advances

POLYMERIZED RAGWEED ANTIGEN E
MAY HELP SUFFERERS OF HAYFEVER

Hayfever sufferers can look forward to fewer and safer desensitization injections, popularly known as allergy "shots", according to National Institute of Allergy and Infectious Diseases grantees at Northwestern University. They have prepared a polymerized form of ragweed antigen E, the major culprit in hay fever, that, when injected, appears to afford the same benefits as the standard pollen extract in about one-third the time and with less risk to the patient.

Densensitization injections are a form of immunotherapy designed to increase a patient's tolerance for the antigen to which he is allergic. The patient receives injections of diluted extracts of an allergen, such as pollen, in increasingly larger doses over a considerable length of time. The size of the largest or maintenance dose depends upon the tolerance of the patient for the extract and the therapy's effect upon his symptoms. The frequency of these maintenance injections may vary from twice a week to once every 2 months, depending on the patient's needs.

Studies by other investigators have shown that antigen E (AgE) is very effective in desensitizing patients allergic to ragweed. With the hope of providing an even more potent material for desensitization, the Chicago scientists synthesized a high molecular weight polymer of AgE by chemically linking together identical AgE molecules. Tests in animals showed that this new polymer is as antigenic as the monomer, single AgE molecules, and that it released from cells much smaller amounts of histamine, an important chemical mediator of allergic reactions.

(more)

HAYFEVER (CONT'D)

To establish the safety of the polymer for humans, the researchers administered it to a small group of patients on the same schedule as that used for standard ragweed immunotherapy. No toxic effects occurred even after a year of therapy. Another group of patients who received doubling doses of polymer until they reached their maintenance level had significantly fewer local and systemic reactions than those receiving comparable doses of the monomer AgE.

In addition, the scientists found that patients who received doubling doses of polymer AgE required an average of 13.3 injections to reach a maintenance level in contrast to 29 injections required by those receiving standard pollen immunotherapy. Patients who received tripling doses of the polymer reached a maintenance level after nine injections, less than 1/3 the number required by standard therapy. The same immunological changes were produced in patients by polymer therapy and standard therapy. All patients showed definite improvements in their allergic symptoms.

Since the maintenance dose can be reached quickly and safely, the scientists feel that a particular advantage to the use of polymer AgE is that patients can achieve effective dose levels rapidly before the start of ragweed season. Furthermore, this concept offers the benefits of immunotherapy to a greater number of patients with less risk and less expenditure of time and money.

The researchers, Drs. W.J. Metzger, R. Patterson, J.S. Irons, J.J. Pruzansky, C.R. Zeiss, and I.M. Suszko, presented their findings at the annual meeting of the American Academy of Allergy in Puerto Rico in March, 1976.

#

Research Advances

NIAID TEAM MAY HAVE GROWN RVL AGENT IN TISSUE CULTURE

National Institute of Allergy and Infectious Diseases (NIAID) scientists believe they may have succeeded in growing in tissue culture the virus already identified as a major cause of acute diarrhea in infants and young children throughout the world.

In 1974, a number of investigators in Australia, England, Canada, and the United States, including NIAID's Dr. Albert Z. Kapikian, reported the presence of a reovirus-like (RVL) agent in stools of young patients with severe diarrhea. In the NIAID studies, conventional and/or immune electronmicroscopy was used to detect the agent's presence and to associate it with the disease. Later, the NIAID scientists reported the successful cultivation of a strain of the virus in human fetal intestinal organ culture.

In the currently reported studies, Dr. Richard G. Wyatt and others in the Laboratory of Infectious Diseases undertook a number of tissue culture experiments, using stool filtrates which had been successfully used to infect the organ cultures. Results of these studies include detection of the RVL agent through 14 passages of one of these filtrates in human embryonic kidney cell cultures. Electronmicroscopy revealed the organism present in the form of subviral particles, lacking the clearly-defined outer capsid.

The laboratory technique of immunofluorescence also revealed the presence of virus in tissue culture passages 11 through 14. Acute and convalescent sera from two infants with RVL-associated diarrhea were tested against the infected tissue culture cells for specificity of fluorescence. Both infants developed serologic evidence of infection by this technique.

(more)

RVL AGENT (CONT'D)

In the final set of experiments, the scientists examined ultrathin sections of tissue culture cells 21 days after inoculation with 13th passaged RVL agent. Electronmicroscopy revealed virus-like particles quite similar in appearance to those previously observed, by other investigators, in duodenal specimens from patients with RVL-associated gastroenteritis.

Although all these results are preliminary, the scientists feel that the newly-isolated virus which they have described probably represents a strain of the human RVL agent capable of at least limited growth in human embryonic kidney cell culture.

A report on these studies has been published in the January 10, 1976 issue of *Lancet* by Richard G. Wyatt, Virginia W. Gill, Mitzi M. Sereno, Anthony R. Kalica, Dale H. Vankirk, Robert M. Chanock, and Albert Z. Kapikian.

#

Research Advances

BIOFEEDBACK TRAINING CAN EASE SEVERE FACIAL PAIN

Biofeedback training that teaches patients to control facial muscles and thereby prevent spasms from occurring in response to stress can help patients with severe facial pain.

Dr. Richard J. Dohrmann of the University of Illinois at the Medical Center in Chicago, IL, described this treatment at the 54th general session of the International Association for Dental Research meeting in March 1976.

Patients with myofascial pain-dysfunction (MPD) syndrome often suffer severe facial pain, muscle spasms, jaw clicking, and limited jaw motion. Theories of the cause and treatment of this disorder vary when there is no pathology in the joint which hinges the jaw to the skull. Studies at the University of Illinois, under the direction of Dr. Daniel M. Laskin, consistently suggest that the pain comes from teeth clenching and grinding. Muscle spasms may result from this response to psychological stress.

The research team, which is supported by a grant from NIH's National Institute of Dental Research, has found that patients obtain relief from several types of treatment including tranquilizing drugs, splints that prevent clenching, and even placebos--especially when the clinician has established such good rapport that the patient has faith in the treatment. Perhaps the promise of relief reduces anxiety and thereby breaks the cycle of tension, clenching, spasms, and pain.

"An advantage of the biofeedback technique," Dr. Dohrmann explained, "is that the patient learns to control muscle tension without medication or such prosthetic devices as tooth guards or splints. Thus, the individual

(more)

gains a sense of accomplishment," he emphasized.

The biofeedback technique teaches patients to relax the masseter muscles which control jaw movement. It enabled 12 of 16 (75 percent) patients to do without further treatment. After six weeks of training, patients said they could relax these muscles during periods of stress and avoid MPD episodes. However, four patients in the experimental group (25 percent) were not helped and required other treatment. Two of these did not respond to any treatment available at the Center.

All 24 persons in the study (16 in the test group and eight in the control group) were given an explanation of the MPD syndrome and told how relaxation of the masticatory muscles could relieve their symptoms. The investigators used electromyograph (EMG) equipment to monitor muscle contraction in both groups, but only the experimental group received feedback--a sound which indicated when the muscles relaxed. Both groups had twelve, 30-minute sessions twice each week for six weeks. All were given instructions for relaxation practice at home. Follow-ups were made six months and one year later.

Of the eight *control* patients, four did not improve with "placebo EMG" nor with any other treatment. (Two in the experimental group were intractable, as well). Three improved sufficiently to require no further treatment. One did not return for follow-up.

In describing the success of biofeedback training, Dr. Dohrmann said, "Although difficult to prove, the patients who seemed to take a more active interest in biofeedback and who took their home practice more seriously appeared to show a greater improvement and to be more pleased with their treatment."

#

Research Advances

SCIENTISTS STUDY TREATMENT OF PERIODONTAL DISEASE

A laboratory test shows that vigorous clinical treatment of subjects with destructive periodontal disease can alter an immune response of their lymphocytes, a type of white blood cell. This type of periodontal disease is the major cause of tooth loss in adults.

The results of the clinical study were reported in March 1976, by a research team from the National Institute of Dental Research at the 54th general session of the International Association for Dental Research.

According to Dr. William E. Wright, lymphocytes normally multiply at a rather slow rate. However, when cultures with foreign substances such as antigens derived from bacterial plaque that forms on teeth, previously sensitized cells are stimulated to grow and divide at a much faster rate. This reaction, called lymphocyte transformation, is the basis of the test.

The investigators' evidence suggests that once a severely diseased individual's lymphocytes are sensitized to substances in dental plaque, "lymphocyte memory" allows the cells to "remember" plaque antigens and respond to them years later.

The investigators evaluated blood samples from 31 individuals. The first group of 20 subjects had destructive periodontal disease that required tooth extractions or surgery to reduce numerous deep periodontal pockets. The 11 other individuals had lost all their teeth years before from severe periodontal disease and had no inflammation in their mouths.

Before treatment, lymphocytes from the first group of patients responded very poorly to dental plaque antigens. However, one month after treatment,

(more)

PERIODONTAL (CONT'D)

which eliminated or sharply reduced plaque accumulations and inflammation, lymphocytes from 15 of the 20 subjects responded. Lymphocytes from the other five subjects remained unresponsive throughout the following year.

When the scientists tested the second group, lymphocytes from 10 of the 11 persons responded strongly to plaque antigens, showing that lymphocytes from subjects without periodontal disease for long periods of time do continue to respond.

When lymphocytes from all 31 subjects were stimulated with an antigen (streptolysin O) not found in dental plaque, all gave a high transformation response. Therefore, the investigators consider that basic immune reactions were operating normally in both groups, and the effect of dental therapy on the transformation of lymphocytes was specific for antigens in dental plaque.

Because the lymphocytes of their severely affected patients did not react proportionally to the severity of the disease, the scientists suggest that the lymphocyte transformation test is not a suitable indicator of a person's current periodontal condition. There was hope that this test might be useful to clinicians because other research had suggested that lymphocyte responses paralleled the progress of the disease. In this study lymphocyte transformation correlates more directly with the subject's history of previous sensitization.

#

April 25, 1976

Research Advances

SPECIAL TRANSFUSIONS ARE TRIED TO AID AML PATIENTS

Victims of acute myloblastic leukemia suffer fewer life-threatening problems with hemorrhaging and infections when their early treatment includes transfusions of histocompatible leukocytes and platelets.

That is one of the initial results of a clinical study being conducted at the Bowman Gray School of Medicine of Wake Forest University, under grants from the National Cancer Institute. The study involves more than 50 patients.

One still poorly understood result of the study, is that patients receiving the histocompatible transusions and intensive chemotherapy have a much higher rate of complete disease remission.

The remissions are most probably the direct result of the chemotherapy and not the transfusions.

Sixty-five percent of the leukemia patients in the controlled study who received the compatible transfusions and the chemotherapy have had complete disease remissions. Other treatments for the disease, involving transfusions of blood cells, not matched for compatibility along with chemotherapy, have shown that only 27 percent of patients attained complete remissions.

According to Dr. M. Robert Cooper, professor of medicine at Bowman Gray, one possible explanation for the improved rate of remissions is that the compatible transfusions strengthen the patient so that more chemotherapy can be given over a longer period of time.

The leukocytes and platelets are very closely matched to a patient's own blood through exactly the same tissue matching techniques used in kidney and heart transplants.

Leukocytes, one form of white blood cells, are transfused to combat

(more)

infections which are the major cause of death in acute myloblastic leukemia patients. The platelets, a crucial factor in blood clotting, are a weapon against hemorrhaging, another cause of death in patients with the disease.

Bowman Gray oncologists think that efforts to fight hemorrhaging and infections should begin before those problems occur. Otherwise, a patient might hemorrhage or become infected and die before the chemotherapy has a chance to work.

In acute myloblastic leukemia, the disease and the treatment act to suppress the body's production of leukocytes and platelets.

The result is that a patient with acute myloblastic leukemia has a greater risk of hemorrhaging, is more likely to develop infections and has less chance of successfully fighting an infection, even with the aid of powerful antibiotics.

Transfusions of incompatible leukocytes and platelets have been given to patients with acute myloblastic leukemia for several years.

But by transfusing histocompatible leukocytes and platelets, there is a greatly reduced chance that the patient's body will reject or destroy the donated blood during the first transfusion or during a later transfusion.

Transfusions of the histocompatible blood cells alone do not provide complete protection against severe infections. The Bowman Gray study has used intensive treatment with antibiotics when infections did develop.

But the study has shown that without the histocompatible transfusions, the antibiotics often are not very effective. The transfusions bolster the body's natural defense against infection so that they can work along with the antibiotics.

Most donors for the transfused cells have been found among the leukemia

(more)

LEUKEMIA (CONT'D)

patients' own families. The blood is taken from the donor and run through a continous flow celltrifuge, (made by AMINCO of Silver Spring, Maryland), which removes the leukocytes and platelets. Red blood cells and plasma are returned to the donor.

During the study, individual donors have not been used more than twice a week. The donors' quickly replaced the leukocytes and platelets removed by the celltrifuge.

Dr. Cooper points out that the process of getting and matching leukocytes and platelets potentially can benefit people other than those suffering acute myloblastic leukemia.

Many drugs used in treating other types of cancers and other kinds of diseases suppress the body's ability to manufacture leukocytes and platelets. And there are diseases other than leukemia which interfere with the manufacture of those same cell components.

#

April 25, 1976

Photo Feature

TREATMENT IS DEVELOPED FOR RAPID PERIODONTITIS

By JEANNETTE BELLIVEAU
University of Maryland Intern

Rapid periodontitis, a dental disorder involving swift bone destruction, red swollen gums, massive plaque and calculus, and painful abscesses, has been successfully treated with tetracycline and gum surgery, reported Sigmund Socransky, D.D.S., of the Forsyth Dental Center in Boston, at a University of Washington (Seattle) seminar.

Periodontal diseases which also include periodontosis and slow periodontitis, are the main causes of tooth loss in persons over 25 years old. The likelihood of some form of periodontal disease increases with age, striking 60 percent of young adults, and 90 percent of persons over 60. Even expensive treatment may fail to save the teeth.

"We have identified several important species of organisms associated with this rapid disease," Dr. Socransky said. "The most ubiquitous is an anaerobic bacterium called *Bacteroides melaninogenicus*."

Periodontal research on antibiotic treatments such as tetracycline has revealed some long-term risk, warn Dr. Socransky and others, including Betsy Williams, Ph.D., of the University of Washington's Center for Research in Oral Biology. The microorganisms in plaque, the gummy buildup of living and dead baceria on the teeth and gums, can become quickly resistant to antibiotics. Some of the resistant organisms can spread throughout the body. Antibiotics would not then be able to combat these more dangerous internal diseases.

Destroying too many bacteria in the mouth by the use of wide-spectrum antibiotics or antiseptics can also harm helpful bacteria. Mouth fungi

(more)

usually kept in check by bacteria, for example, can thrive in the environment vacated by the destroyed microorganisms.

"The mouth is a complex ecosystem and functions like a forest or any other part of the environment," said Dr. Williams. "Recent research suggests that it may be possible to eliminate certain bacteria, shown to be involved in disease, provided that at the same time a less virulent species is introduced to take over many of the functions of the absent organisms. We want to work on this as an alternate means of plaque control for the prevention of disease."

Dr. Williams has catalogued 1,500 strains of bacteria found in pockets around teeth below the gum surface and is attempting to find out which microorganisms are helpful and which harmful. She is particularly concerned with anaerobic bacteria, since a higher percentage of these are found below the gums.

"Anaerobic bacteria can't live in the presence of oxygen," she said. "Some die within seconds of exposure to air. To study them, you need a completely oxygen-free environment. I am using an anaerobic chamber for this purpose that has become available only within the last few years."

Both Dr. Williams and Dr. Socransky have found mysterious new organisms that don't fit standard classifications, which list bacteria according to appearance, need for the presence or absence of oxygen, and ability to ferment various substances. This shifting spectrum requires microbiologists to create new classifications for bacteria.

Dr. Williams compared genes in the organisms to identify and classify

(more)

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TREATMENT (CONT'D)

related groups.

"What we are looking for," she said, "is not just the identity or behavior patterns of one or two microorganisms. We want to find out which bacteria produce biochemical substances that may begin the disease process, probably by provoking certain pathological immune responses."

While several lines of research proceed, oral scientists are trying to learn the best defense against plaque, the primary cause of cavities and periodontal disease. So far, the most effective defense is still rigorous toothbrushing and flossing.

The research of Dr. Socransky and Dr. Williams, and the University of Washington's Center for Research in Oral Biology, is supported by the National Institute of Dental Research.

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TREATMENT (CONT'D)

Dr. Betsy Williams classifies the thousands of bacteria associated with periodontal diseases, with the help of an anaerobic chamber. (NIH Photo #1546)

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Photo Feature

RESEARCHERS SEEK SAFER ANTIVENIN

Undergraduate biomedical researchers at Texas A&I University in Kingsville, Texas, may be on the track to the development of an antivenin which will eliminate the dangers of adverse reactions by snakebite victims to antivenin now in use.

Developing a method through which antivenin can be purified, the investigators are testing the substance for effectiveness and safety in its use in snakebite cases.

A report on the characterization of venom was made at the Fourth Annual Xavier--MBS Biomedical Symposium, cosponsored by NIH's Division of Research Resources and Xavier Univerisity of Louisiana, April 5-7, 1976 in New Orleans.

The snake venom research has been conducted for nearly two years at A&I under the direction of Dr. John Perez. Aided by a grant from the National Science Foundation, the research is done by participants of the Minority Biomedical Support program.

The antivenin currently in use for bite victims is a horse serum which contains other antibodies besides the snake antivenin material. This serum can cause problems for people who are naturally allergic to horses or who have had contact with previous doses of the serum.

The purification process used at A&I takes out the unneeded antibodies, leaving only the desired material which will alleviate the adverse reactions by users of the antivenin.

The purified substance is being tested in laboratory animals to observe its effectiveness and check for any adverse reactions.

(more)

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VENOM (CONT'D)

The venom used in the process is gathered from rattlesnakes which are kept in glass-front cages in the animal laboratory on the A&I campus. The snakes are varied in size, and many are captured in the South Texas area by students.

Most of the snakes have come to A&I from the annual Rattlesnake Roundup held near Freer in Duval County. Many other snakes caught in the roundup are "milked" of their venom and released.

The captive snakes are milked every two weeks and returned to their cages with white mice as a reward.

A spinoff of the antivenin study is a behavioral study on the rattlesnakes. Their eating habits are observed, the amount of venom produced and the duration of venom productiveness are noted, and their reproductive ability in captivity is recorded.

To add the necessary antibodies to neutralize the poisonous snake venom, the A&I biology department maintains a herd of goats which have been injected with rattlesnake venom. The antibodies and proteins in the animal system which combat the venom are extracted and added to the snake venom insolubilized into a jelly-like substance.

The two substances are then centrifuged and washed, a process which enables the antivenin compound to be extracted from the other proteins leaving a purified substance.

The antivenin purification program is part of the biomedical research and training programs at A&I which are supported by NIH's Minority Biomedical Support program.

(more)

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VENOM (CON'T)

The overall studies program is funded by a $200,000 grant from the National Institutes of Health through its Division of Research Resources.

Other projects are in the areas of viral research, cell physiology, genetics, and bacteriology.

Venom drips from the business end of a Texas rattler as Texas A&I University researchers collect the poisonous substance for antivenin study. Snakebite victims suffer adverse reactions from commonly used horse serum antivenin. The investigators are attempting to eliminate foreign protein substances in the antivenin. A progress report on the research project was made at the Fourth Annual Xavier-MBS Biomedical Symposium, cosponsored by NIH's Division of Research Resources and Xavier University of Louisiana, in New Orleans in early April. (NIH Photo #1547)

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NEWS & FEATURES From NIH April 25, 1976

News Feature

MRFIT PROMISES TO BE IMPORTANT HEART STUDY

Enrollment of volunteers has been completed for a major clinical trial to evaluate what effect lowering blood cholesterol, reducing elevated blood pressure, and curbing cigarette smoking has in prevention of first heart attacks and in reducing death rates from coronary heart disease (CHD) and other cardiovascular disorders, according to Dr. Robert I. Levy, Director of the National Heart and Lung Institute.

Called the Multiple Risk Factor Intervention Trial (MRFIT), the NHLI-supported study involves 20 participating centers around the country and more than 12,500 volunteers. The clinical phase of the study will run for six years at an estimated cost of approximately $12 million a year.

More than 366,000 men were screened to select out and enroll the 12,500 who will participate in the study. These are men, aged 35-57, who do not have clinical evidence of coronary heart disease, but are at higher than average risk of developing it because of various combinations of elevated blood cholesterol, high blood pressure, or cigarette smoking.

Any one of these factors roughly doubles CHD risk, and the presence of all three may increase risk more than tenfold. Because of various combinations of these three risk factors, the risk of the MRFIT participants selected was estimated to be higher than that of about 90 percent of the 366,000 people screened for the study.

The other important thing about these three risk factors is that all three can be modified or eliminated. Elevated blood cholesterol and high blood pressure can be effectively treated. Cigarette smoking, a pernicious but often cherished vice, can be curbed or eliminated.

(more)

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MRFIT (CONT'D)

In selecting volunteers for the study, potential participants were asked to fill out a brief medical questionnaire and had their blood cholesterol and blood pressure levels checked at the primary screening visit. At two subsequent screening visits, potentially eligible men received more extensive examinations.

Those selected for enrollment in the study have been divided at random into two groups. Half were referred to their personal physicians or usual source of medical care (together with the results of the screening tests) and invited to return to the Clinical Center each year for a cardiovascular examination. The other half enter a Special Intervention program, designed to:

- reduce blood cholesterol levels by dietary means
- lower elevated levels of diastolic blood pressure by weight reduction and medication
- eliminate cigarette smoking.

The interventions in this group involve changing some living and health habits, and thus have a strong educational component. Since changes in health-related behavior are sought, behavioral scientists are working closely with physicians and nutritionists.

The goal of the Multiple Risk Factor Intervention Trial is to answer a critical question as yet unanswered by direct experiment: Can the reduction of these three common risk factors for coronary heart disease prevent heart attacks and premature death in a segment of the U.S. population who are at high risk?

Planning, organizing and implementing the study was begun in 1972. A Steering Committee of the principal investigators in the study is chaired by Dr. Oglesby Paul, Professor of Medicine, Northwestern University, Chicago.

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MRFIT (CONT'D)

In addition to the 20 clinical centers the Program also includes a coordinating center; a central laboratory; an electrocardiographic center; and professional supporting activities from the National Heart and Lung Institute, the National Center for Disease Control, and the Drug Supply Center of the PHS at Perry Point, Maryland.

Staffing of each clinical center includes a cardiologist for diagnostic evaluations,and nutritionists to help in formulating and supervising dietary changes for reduction of blood cholesterol levels. Also, behavioral scientists will assist in the program for smoking cessation, and will be helping participants make other changes in living patterns to reduce the risk of CHD. Physicians direct the management of hypertension intervention and supervise the medical aspects of the study.

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April 25, 1976

News Feature

POSSIBLE LINK SEEN BETWEEN DIABETES AND THYROTOXICOSIS

Grantees of the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD) have obtained additional evidence of an inherited relationship between diabetes and thyrotoxicosis, a form of hyperthyroidism, and suggest testing all thyrotoxic patients for glucose intolerance.

Although an association between glucose intolerance and thyrotoxicosis was first reported over 100 years ago, the importance of this relationship remains unclear. In 1965, NIAMDD grantees Dr. Harvey C. Knowles, Jr. of the University of Cincinnati and associates, reported hyperglycemia "consistent with diabetes mellitus" in 29 of 51 thyrotoxic patients (57 percent), and proposed an inherited relationship between diabetes and thyrotoxicosis.

Long-term observations of 22 of these 51 patients now have provided further support for this hypothesis, and have suggested that initial testing of all thyrotoxic patients for glucose intolerance is advisable. Moreover, all thyrotoxic patients displaying diabetes glucose intolerance when undergoing successful antithyroid treatment should be considered to have permanent diabetes until proved otherwise.

Adequate follow-up data were obtained in 22 of the original group of 51 patients. These subjects had evaluations performed for glucose tolerance while thyrotoxic, and at mean follow-up times of 8.8 months and 11.6 years after adequate antithyroid treatment.

Seven of 22 patients (32 percent) demonstrated glucose intolerance more than ten years after successful treatment for thyrotoxicosis, and the glucose intolerance appeared to be clinically important in five of the seven patients. In addition, a family history of diabetes, or a history of children with birth

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NIAMDD (CONT'D)

weight greater than 9.02 pounds, or both, was present in 10 of 22 patients (43 percent), which is more than double the prevalence for these observations in the general population.

All but one of the patients with clinically important glucose intolerance at ten year follow-up had a diabetic glucose tolerance test while thyrotoxic, and 50 percent of the latter had clinically important diabetes ten years later. Thus, the investigators advocate testing all thyrotoxic patients for carbohydrate intolerance and closely following those who demonstrate abnormal tolerance.

Dr. Knowles, Jr., of the University of Cincinnati and associates reported their findings in the *Archives of Internal Medicine*.

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NEWS & FEATURES From NIH

April 25, 1976

Photo Feature

NIH SCHEDULES PUBLIC OPEN HOUSE MAY 1-2

The National Institutes of Health (NIH) will hold an Open House for the public from 10:00 a.m. to 4:00 p.m. on Saturday and Sunday, May 1 and 2, 1976.

The Open House, scheduled as part of the Department of Health, Education, and Welfare's observance of the Nation's Bicentennial will take place on NIH's 300 acre "campus" in Bethesda, Maryland, located on Rockville Pike, twelve miles northwest of the nation's Capitol.

Visitors will be able to see research exhibits, tour laboratories, hear scientist speakers, and view health films. One attraction will be the "NIH Health Research Trail," the first stop of which is located in front of the main administration building (Building One) -- an outdoor walk-through abstract "Cell." This unique, colorful art form serves to emphasize the importance of biomedical research, not only into the mysteries of the cell, but in the conquest of disease. The Hippocrates tree, actually raised from a seedling of the original, is a part of the trail.

Exhibits include typical research animals, a germ-free animal tank, scientific glass blowing, eyeglasses that simulate the effects of visual diseases, facts about genetic diseases, a whiplash model and the effects of serious injury to the nervous system.

In a series of scheduled lectures for the public, experts will talk about child health, reducing cancer risk, healthy lungs, heart attacks, mental depression, acute leukemia, kidney disease, and diabetes and obesity.

Health films will cover such topics as understanding the human body, maintaining good health, recent advances in disease research, modern health

(more)

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OPEN HOUSE (CONT'D)

care techniques, and careers in health professions.

Tours will also be conducted through major facilities of the NIH Clinical Center, including clinical pathology, blood bank, medical records, pharmacy, clinical and management systems, and nuclear medicine.

An exhibit covering 200 years of medicine will be on display at NIH's National Library of Medicine.

A wide array of public information materials on health and disease will be available without cost to visitors. Free high blood pressure and visual acuity tests will also be available. Employee hosts and hostesses will help explain the agency's work.

Cafeterias will be open and picnic tables will be provided for those who want to bring their own lunch. Free shuttle buses will tour the campus and there will be provision for the handicapped.

An Open House Guide Book is available. Write NIH Visitors Center, Bethesda, Maryland 20014, or phone (301) 496-1776.

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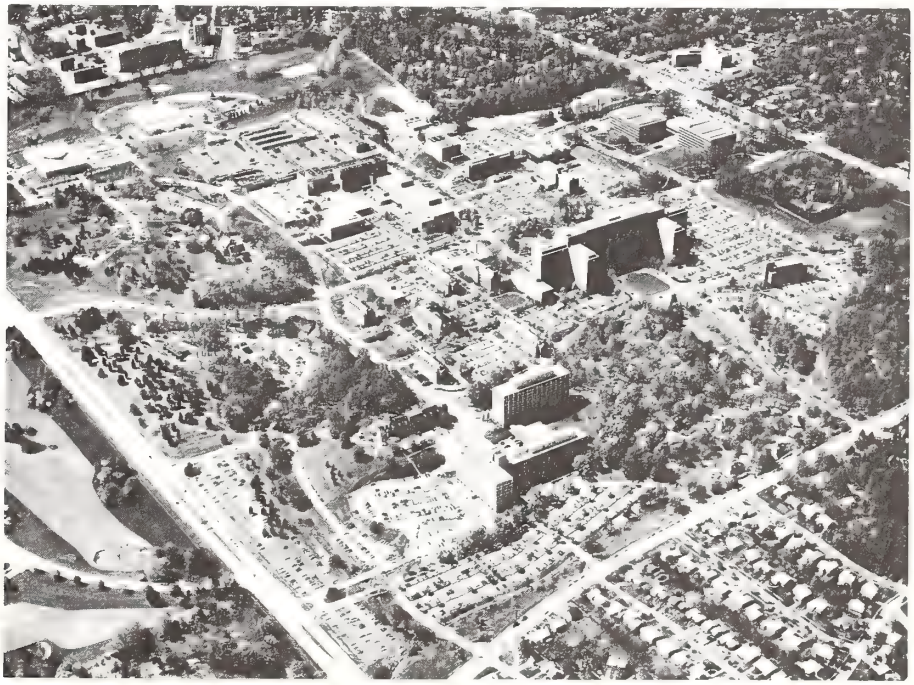

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News Feature

DHEW PROPOSES NEW PEER REVIEW RULES

The Department of Health, Education, and Welfare announced on March 29, 1976, proposed regulations governing scientific peer review of proposals to conduct biomedical and behavioral research.

The proposed regulations codify the present system of review of grant applications under the Public Health Service Act administered by the National Institutes of Health (NIH), the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA), and the Food and Drug Administration (FDA). They further establish uniform rules for peer review of all research and development contract project administered by the three agencies.

The proposed regulations were published in the *Federal Register*.

The regulations include rules regarding the composition of peer review groups and protection against conflicts of interest. They also outline criteria for the review of grant applications.

These provisions also apply to research and development contract projects. However, in establishing the matters to be reviewed and the criteria to be employed, distinctions are drawn between solicited and unsolicited contract proposals.

Interested persons are invited to submit written comments concerning the proposed regulations. Inquiries may be addressed, and data, views and arguments relating to the regulations presented in writing (in triplicate) to the Associate Director for Extramural Research and Training, Building One, Room 118, 9000 Rockville Pike, Bethesda, Maryland 20014.

Comments received will be available for public inspection at this Office on weekdays (Federal holidays excepted) between the hours of 8:30 a.m. and 5:00 p.m. All relevant material received on or before May 28, 1976 will be considered.

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April 25, 1976

Research Illustrated

NLM PRESENTS SPECIAL BICENTENNIAL EXHIBIT

In recognition of the nation's Bicentennial, the National Library of Medicine is presenting an exhibit highlighting selected American achievements in medical science and practice and outlining the development of medical education, medical literature, and public health in the United States.

The exhibit is installed in the lobby of the Library, located at 8600 Rockville Pike, Bethesda, Maryland, and will remain through 1976. Members of the public are welcome.

The display features books, manuscripts, and pictures from the Library's collections, including John Jones' *Plain, Concise, Practical Remarks on the Treatment of Wounds and Fractures* (1775) and other works by physician-patriots. One case highlights a letter from George Washington about the medical department of the Army. Another section presents a capsule history of NLM. An illuminated panel displays portraits of 29 American men and women who have made notable contributions to medicine through the years. A selection of fine prints illustrates changing views of the American physician through the eyes of the artist.

Also included in the exhibit is a patent model of William T.G. Morton's ether inhaler (on loan from the Smithsonian Institution) and a microscope used by Joseph J. Woodward in his early photomicrography studies (on loan from the Armed Forces Medical Museum).

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Charles R. Drew (1904-1950), of Washington, D.C., was a graduate of Amherst and received his M.D. from McGill University in 1933. He took further training at the Royal Victoria Hospital and Montreal General Hospital, Freedmen's Hospital in Washington, and Columbia-Presbyterian Hospital in New York City. At Columbia the study of blood plasma and blood preservation became his major effort. His research made him the logical choice to direct the "Blood for Britain" program in 1940 and in 1941 he was appointed assistant director of the blood procurement program for the National Research Council with the responsibility of providing blood for use by the American military forces. At that time the Red Cross donor program was segregated. The black man's blood could not be transfused to the white. This was an untenable position for Drew and he resigned his directorship of less than a year as the blood procurement program was about to become nationalized. He accepted the position of professor and head of the department of surgery at Howard University in October 1941. His qualities of a teacher and his contributions to the surgical residency program placed the Howard training program on a firm foundation. His further contributions to surgery and blood preservation were cut short by his untimely death in an auto accident at the age of 46. (NIH Photo #1548)

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Joseph Goldberger (1874-1929), a member of the U.S. Public Health Service from 1899 until his death, was an extremely gifted epidemiologist. In 1914, he was placed at the head of a team to study pellagra, which had become increasingly prevalent in the southern United States after 1900. By 1914 most physicians felt it was of infectious origin. Golberger through numerous field studies and experiments proved the disease to be due to a dietary deficiency. Although he died before the specific dietary substance necessary for prevention could be isolated, he did know that diets with ample amounts of milk, fresh meat, butter, and eggs could prevent or cure the disease. This P-P (pellagra-preventing) factor was isolated and identified as nicotinic acid in 1937. (NIH Photo #1549)

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(more)

NLM (CONT'D)

Silas Weir Mitchell (1829-1914) was a noted poet and novelist who was, above all, a superb clinician. During the Civil War, with George R. Morehouse and William W. Keen, he made studies of gunshot and other injuries of peripheral nerves which were afterward expanded in his important work, Injuries of Nerves and Their Consequences (1872). *Mitchell was the first to describe causalgia, post-paralytic chorea, and other neurological conditions. His origianl and important research in neurophysiology included studies on the coordination functions of the cerebellum. (NIH Photo #1550)*

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(more)

NLM (CONT'D)

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Mary Adelaide Nutting (1858-1948), was one of America's leaders in professional nursing and nursing education. She was a graduate of the first class of the Johns Hopkins Hospital Training School for Nurses in 1891. She became the second superintendent of nurses and principal of the Hopkins School of Nursing in 1894. In 1901 she was the first to develop a sound preliminary program for nursing students, emphasizing principles of nursing, before plunging them into actual hospital training. She was an important early figure in the American Society of Superintendents of Training Schools for Nurses and struggled long and hard to establish professional standards for nursing. She carried on a life-long crusade to bring the education of nurses within universities. In 1907 she accepted a full-time professorship at the Teachers College of Columbia University and in 1910 became chairman of the Department of Nursing and Health. She exerted a greater influence on the development of nursing education than any other individual of her time. (NIH Photo #1551)

Editors of publications may request a glossy print of the numbered photographs that appear in this issue.

Ms. Joyce Flaherty
National Institutes of Health
Building 31, Room 2B-10
Bethesda, MD 20014

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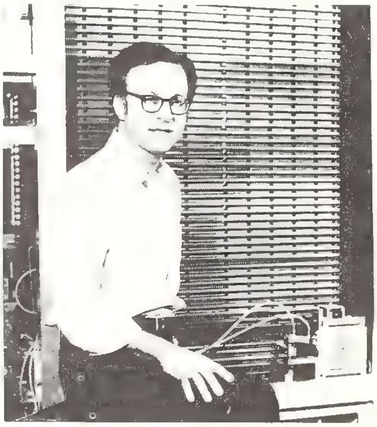

See page 15

RESEARCH ADVANCES:

Four-Drug Combination Can "Cure" Hodgkin's Disease.....1
Method Reported to Detect Oral Cancer in Early Stages.....4
Viral Agent Seen as Major Cause of Severe Diarrhea.6
MS Patients' Brain Tissue Seems to Contain Small Virus.....9
Fluoridated Water Brings More Impressive Benefits.....12
Value of Various Doses of Methotrexate Compared.....14

NEWS AND PHOTO FEATURES:

Advanced Technique Found for Processing Cultures.....15
Scientists Evaluate Four Tests for "Mono".....19
Progress Made in Understanding Cause of Chagas' Disease.....21
Dental Researchers Continue Investigation into Saliva.....23
Orthodontia for Adults Seen as a Possibility.....25

DISEASE PROFILE:

NCI Is Studying a Rare Skin Disease.....26

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Research Advances

FOUR-DRUG COMBINATION CAN "CURE" HODGKIN'S DISEASE

Advanced Hodgkin's disease is curable with a four-drug combination (MOPP) in more than half of all treated patients, Dr. Vincent DeVita, Jr., Director of the Division of Cancer Treatment, National Cancer Institute (NCI), reported to the 12th annual meeting of the American Society of Clinical Oncology, on May 5 in Toronto. His findings were based on ten-year survival data from a study conducted in the NCI's Medicine Branch.

Hodgkin's disease is a malignant disease of the lymph glands. While early stages of the disease, those limited to a confined area of the body, can be treated effectively with radiation therapy, fewer than 10 percent of patients with advanced disease have survived five years when treated with either radiation therapy or single anticancer drugs. Virtually no patient with widespread disease--Stages III and IV--survived free of disease beyond five years.

A treatment program for advanced Hodgkin's disease, consisting of four drugs (Nitrogen mustard, Vincristine (Oncovin^R^), Procarbazine and Prednisone, called MOPP) was begun at the National Cancer Institute in 1964. "We now have ten-year follow-up data on 194 patients treated with this program," Dr. DeVita said. None of the 194 patients included in the analysis had significant therapy prior to receiving MOPP.

Eighty-one percent (155 of 194) of patients treated with MOPP achieved a complete remission--disappearance of all evidence of disease. This is a fourfold increase over remissions achieved with single drugs, Dr. DeVita said. Of the 155 patients who achieved a complete remission, 82 percent are alive

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at five years after all treatment was stopped, and 72 percent of those patients at risk are alive at 10 years. Sixty-six percent of these patients are in their first complete remission at five and 10 years. In sharp contrast, no patient who failed to achieve a remission with MOPP is alive at five years.

Dr. DeVita and his colleagues analyzed the data for factors that might influence the completeness of a patient's response to the multiple-drug chemotherapy. These factors include age, sex, stage of disease when treated, microscopic appearance of the lymph node (histology), involvement of organs other than those in the lymphatic system and presence of absence of symptoms.

Symptoms of Hodgkin's disease that usually appear in later stages of the disease include fever, weight loss, and night sweats.

The presence of these symptoms was the only factor that influenced the ability of a patient to achieve a complete remission, Dr. DeVita said. Fully 100 percent of the 22 asymptomatic patients achieved a complete remission, while 77 percent of patients with symptoms achieved a complete remission.

Duration of the first complete remission was also influenced by the presence of symptoms. All 22 asymptomatic patients remain in their first remission at five years, while 60 percent of patients with symptoms are in complete remission at five years. Histology also played a role in the continuous disease-free status, Dr. DeVita noted. Patients with nodular sclerosing Hodgkin's disease had shorter complete remissions than patients with either of the other three histologic variants: mixed cellularity, lymphocyte depleted or lymphocyte predominant.

Because nodular sclerosing is a more indolent form of the disease, overall

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survival was not affected by histology at either five or ten years. Poorer survival did correlate with the presence of symptoms, however.

Median survival, the length of time that half of the population of patients lives, has not been reached in the study. Sixty-five percent of all 194 patients are alive at five years and 58 percent at ten years. No one who has remained in complete remission for 42 months following treatment has relapsed.

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Research Advances

METHOD REPORTED TO DETECT ORAL CANCER IN EARLY STAGES

Early detection of oral cancer, when chances of cure are the greatest, is improved by biopsy of red, velvety lesions in three, specific, high risk regions of the mouth. A Veterans Administration oral surgeon has reported that erythroplastic (red) lesions, especially those with white speckling, are suspect when they occur on the floor of the mouth, on the sides or undersides of the tongue, or on the soft palate complex.

Arthur Mashberg, D.D.S., of the East Orange, N.J., VA hospital and Lawrence Garfinkle, of the American Cancer Society, discovered these criteria in a prospective study of asymptomatic lesions. Those lasting two weeks or more were biopsied regardless of color or size.

Details of this study, which is supported by NIH's National Institute of Dental Research, are described in the May issue of *Cancer*, the Journal of the American Cancer Society. In the article Dr. Mashberg and Harry Meyers, D.D.S., of the same VA Hospital, report that 97 percent of the 207 intra-oral squamous cell carcinomas found in 161 patients were located in three soft tissue areas: 49 percent on the floor of the mouth, 30 percent on the soft palate area (the soft palate-anterior pillar-retromolar trigone complex), and 18 percent on the sides or the underside of the tongue.

The research also showed that the appearance of most early tumors was a red lesion with white specklings. The next most frequent type was red with no white areas. Very few were classified as all white.

These findings are contrary to the widely-held view that most precancerous or cancerous lesions in the mouth are white. The investigators believe that the traditional description of oral cancer--lumps, ulcers, bleeding, swelling,

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and pain--apply to more advanced cases, which have a much lower five-year survival rate. The investigators recommend that when evaluating risks, age and oral habits be considered; most patients found to have oral cancer in this study were middle aged, heavy drinkers and smokers.

A large percentage (72 percent) of the cancerous tumors found were invasive, despite their innocuous appearance and small size. Of those that were invasive, most (82 percent) were 2 cm or less in diameter, with many (39 percent) being 1 cm or less. Nevertheless, nearly all of these 161 patients have a good chance of recovery from oral cancer with minimal facial deformity because only three of them had lymph node involvement related to the oral lesions.

Dr. Mashberg suggests that the cancer classification be altered to include lesions of 1 cm or less, explaining that by observing the exisiting classification, many examiners might bypass lesions less than 2 cm.

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Research Advances

VIRAL AGENT SEEN AS MAJOR CAUSE OF SEVERE DIARRHEA

Scientists at NIH's National Institute of Allergy and Infectious Diseases (NIAID), at Children's Hospital National Medical Center, Washington, D.C., and at Johns Hopkins Hospital, Baltimore, have provided further strong evidence that a viral agent -- HRVL (human reovirus-like) -- is the major cause of severe diarrhea in infants and young children during the winter months.

Their study also indicated that toxin-producing strains of *Escherichia coli* -- a bacterium associated with diarrhea -- are probably of little importance in gastroenteritis of early childhood.

In addition, Dr. Albert Z. Kapikian, NIAID, and Dr. Hyun Wha Kim, Children's Hospital, and their co-workers found that one important mode of transmission of the disease may be from parent to child since HRVL infection was detected in 35 percent of a group of parents studied.

Sporadic infantile gastroenteritis is an important disease throughout the world. It occurs predominantly in infants and young children and may require hospitalization and intravenous feeding. In a survey of a sample of U.S. pediatricians, it was found that gastroenteritis was the second most common illness of their patients. (First were respiratory infections.)

In the present study, during the period January 1974-June 1975, 143 infants and young children admitted to Children's Hospital with acute diarrhea were carefully examined in an effort to determine the cause of their illness. The team of scientists used electron microscopy and/or serologic techniques to detect HRVL presence or evidence of infection in fecal specimens and blood taken from the young patients.

Overall, 67 (47 percent) of the 143 patients were found infected with HRVL.

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The scientists were surprised to find that, in this survey, electron microscopy was equal in sensitivity to the serologic technique of complement fixation in detecting HRVL infection. In most virus infections, serologic methods are more efficient than virus isolation methods that use cell culture systems. The complement fixation test for HRVL was developed by Dr. Kapikian's group, using a HRVL-rich specimen as antigen, if available, or a related calf diarrhea virus as a substitute antigen. The availability of two reliable techniques -- electron microscopy and complement fixation -- should greatly facilitate epidemiologic and diagnostic studies, with laboratories free to use the method best suited to individual field conditions.

HRVL infection in the Children's Hospital patients had a seasonal pattern. Fifty-nine percent of those admitted during the cooler months (November to April) shed HRVL, with a peak in December 1974-January 1975, combined. None of the patients admitted during the warmer months (May to October) shed the agent.

Of special concern to the scientists was determination of the role of toxin-producing strains of *Escherichia coli* in causing illness in their study patients, since such organisms have been associated with diarrhea in both children and adults. Although 71 percent of the Children's Hospital patients were found to harbor at least one potentially pathogenic virus or bacterium, no toxin-producing *E. coli* were found in a survey of 32 of the patients.

When HRVL antibody was present in the blood, the HRVL agent frequently could not be found; but a protective role for such antibody could not be established. Illness often occurred in spite of the presence of antibody -- a finding

(more)

consistent with results of other studies of diarrheal disease in newborn monkeys and in calves. The scientists stress that they need to know more about immunologic mechanisms involved in protection against HRVL before attempting to develop a vaccine to prevent the illness.

Authors of the report in the April 29, 1976, issue of the *New England Journal of Medicine* are: Albert Z. Kapikian, M.D., Hyun Wha Kim, M.D., Richard G. Wyatt, M.D., W. Lee Cline, Julita O. Arrobio, M.D., Carl D. Brandt, Ph.D., William J. Rodriguez, M.D., David A. Sack, M.D., Robert M. Chanock, M.D., and Robert H. Parrott, M.D.

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Research Advances

MS PATIENTS' BRAIN TISSUE SEEMS TO CONTAIN SMALL VIRUS

Investigators partially supported by the National Institute of Allergy and Infectious Diseases (NIAID) have confirmed and extended work by others showing that brain tissue and sera from multiple sclerosis (MS) patients contain what appears to be a small virus. Although the role of this Multiple Sclerosis Associated Agent (MSAA) remains to be determined, the scientists, led by NIAID Career Awardee Werner Henle, say it should be considered a candidate for the causation of this disease.

Viruses, as well as a host of other factors, have long been suspect as causing MS, a progressive, crippling disease of the central nervous system which may alternately flare up and subside. About 500,000 people in the United States suffer from MS and closely related disorders.

The existence of MSAA was first reported in 1972 when injections of mice with material from MS patients caused depressions of white blood cells called polymorphonuclear leukocytes (PMN). A drop in the number of these cells is considered indicative of the presence of an infective agent. Other investigators, however, had not been able to confirm these results.

In the presently reported studies, PMN depressions were again seen in mice, as well as in rats, hamsters, and guinea pigs injected with material from MS patients. The agent causing the depressions was found to multiply at high titers in central nervous tissues of inoculated animals and could be serially transmitted from animal to animal. The possibility of MSAA being an indigenous experimental animal virus was negated by a number of research results, including failure of materials from non-MS patients and mouse brains to cause PMN

(more)

depressions.

All eight brain homogenates from autopsied MS patients caused PMN depressions, while 11 control suspensions from autopsied non-MS patients failed to do so. Not all sera from MS patients contained MSAA. Its presence seemed dependent on the patient's clinical state, those with active disease showing 73 percent positive results, and those in remission 31 percent.

Spinal fluid from eight MS patients neutralized the MSAA, rather than depressing PMN's, indicating antibody activity. Of 23 sera from nursing staff and relatives of MS patients, 26 percent were highly positive for this MSAA-neutralizing activity, and only 35 percent were negative. Of sera from 59 American donors not known to be associated with MS patients, only one was positive. However, 23 percent of East African sera from donors under 15; and 67 percent from those over 50 showed MSAA-neutralizing capability.

The authors draw a parallel between multiple sclerosis and infectious mononucleosis. Both diseases, they say, occur predominantly in middle and upper class adolescents and young adults in economically advanced countries, and both diseases are rare in underdeveloped countries. The Epstein-Barr (EB) virus, believed to be responsible for infectious mononucleosis, causes mild early infections in underdeveloped countries. Conversely, in advanced countries, these infections are often delayed and appear later as clinical infectious mononucleosis. Since a large number of sera from East Africans neutralized MSAA and sera from Americans did not, the authors suggest that the same pattern could hold for multiple sclerosis. The ability of sera from MS relatives and nursing personnel to neutralize MSAA implies, they say, that, like EB virus infections, not all MSAA infections result in clinical disease.

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MS (Cont'd)

These findings were presented in two papers in the December 1975 issue of *Infection and Immunity*, by Drs. Werner Henle, Gertrude Henle, Ursula Koldovsky, Paul Koldovsky, Rudolf Ackermann, and Gunter Haase from the Joseph Stokes, Jr. Research Institute, the Children's Hospital of Philadelphia and School of Medicine, University of Pennsylvania.

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Research Advances

FLUORIDATED WATER BRINGS MORE IMPRESSIVE BENEFITS

Dental scientists gathered at the 54th general session of the International Association for Dental Research meeting in Miami Beach, FL, heard in March 1976 that the amount of tooth decay which remains in a community with properly fluoridated water was reduced by two-thirds in children treated with a combination of five techniques.

"The reduction in tooth decay is impressive," Dr. Robert A. Bagramian of the University of Michigan commented, "especially when you realize that fluoridating the community water supplies in Ypsilanti and Willow Run, Michigan, already has reduced incidence of tooth decay by about 60 percent."

To determine the benefit of using several available preventive measures regardless of their cost, the children had their teeth cleaned, the chewing surfaces coated with a plastic sealant, a fluoride gel applied twice a year, supervised instruction in daily personal care of teeth, and all decayed teeth, filled.

Last year Dr. Bagramian reported that one year after the preventive treatments were begun, the children in the test group had 85 percent less new tooth decay than children in the comparison group, which received only the personal oral hygiene instruction. Second year results, which are being presented this year, were somewhat less dramatic, but still showed a 60 to 70 percent reduction.

Although this "intensive Care" type of approach was effective, its cost in skilled personnel decreases its usefulness as a public health measure. Therefore, the National Caries Program (NCP) is still seeking new agents to

(more)

fight tooth decay and is trying to develop a sealant that is more durable and easier to apply.

The sealant used in this three-year study, supported by a contract from the NCP, National Institute of Dental Research, is a plastic resin that is painted onto the decay-prone chewing surface of teeth. It looks like colorless nailpolish but does not harden until ultraviolet light is focused on it. Thus, the fluid reaches the botton of the tiny pits and grooves on the tooth surface before it hardens.

A van equipped with two dental operatories and X-ray equipment went to elementary schools in Ypsilanti and Willow Run, where first and sixth graders participated in the study. All children were examined for tooth decay and were divided into a treatment and a comparison group. At the beginning of the study, decay prevalence was similar in each group.

Every six months, the teeth were examined to see if the sealant had been lost and it was re-applied where needed. Clinical and X-ray examinations were made once a year to detect new cavities. Decayed teeth were filled when appropriate.

#

Research Advances

VALUE OF VARIOUS DOSES OF METHOTREXATE COMPARED

Some human tumors might be treated more effectively with a higher dose of methotrexate, a common anticancer drug, than the dose effective against certain animal tumors, NIH scientists have reported.

Dr. Richard A. Bender of the National Cancer Institute, discussed the research on May 7, 1976, at the 67th Annual Meeting of the American Association for Cancer Research in Toronto.

Dr. Bender and his colleagues treated laboratory-grown animal tumor cells with different concentrations of methotrexate. They measured the concentrations of the drug within the cell (intracellular concentration) and the rates of DNA (deoxyribonucleic acid) synthesis. DNA, the hereditary material in the nucleus of each cell, must be synthesized for cells to grow.

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Methotrexate inhibits DNA synthesis by blocking the action of a necessary enzyme. The intracellular concentration of methotrexate that had the greatest impact on DNA synthesis also was the concentration at which methotrexate's target enzyme was inhibited the most.

As human leukemia cells have DNA synthesis inhibited at lower methotrexate concentrations, individual tumor thresholds are suggested. Their latest studies show that some animal tumor cells are able to absorb the drug in greater concentrations than the surrounding tissue culture fluids. Human tumor cells do not seem to concentrate the drug, however.

To achieve the same intracellular concentration of methotrexate in human tumor cells as in animal cells, a larger concentration of extracellular methotrexate might be required.

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May 25, 1976

Photo Feature

ADVANCED TECHNIQUE FOUND FOR PROCESSING CULTURES

A major national resource is being developed at the University of California, Berkeley, which will allow cell biologists to process up to 100 million cultures at once, subjecting them to controlled environments with automatic surveillance and screening for mutants in accordance with computer-programmed instructions.

The utilization of this new technique for producing, identifying, and isolating many thousands of microbial or animal cultures simultaneously under rigidly controlled environmental conditions promises to accelerate biomedical investigations in a number of health-related areas.

Invented and developed by Dr. Donald A. Glaser, Professor of Physics and Molecular Biology at the University of California, the mass screening cell culture machine is two stories high and forty feet long. The current major funding for the facility--approximately $1.7 million over three years--comes from NIH's Division of Research Resources.

The Glaser system known as "the Dumbwaiter" is a refinement and enlargement of his previously designed cell processing apparatus called "the Cyclops machine." Dr. Glaser is a 1960 Physics Nobel Prize winner, receiving international recognition for his work in inventing "the Bubble Chamber," which records tracks of elementary particles.

The basic elements in the Dumbwaiter system are two stacks, containing 64 aluminum frames each, and joined by two horizontal cross-ducts. Each aluminum frame carries two glass trays with an open area of about 40 x 80 cm which circulate through the machine by rising one step at a time throught one stack, crossing over through the top tunnel to the other stack, down the second stack, and across the bottom cross-duct to return to the original stack.

(more)

CULTURES (Cont'd)

This machine, called the Dumbwaiter for obvious reasons, is a sterile incubator whose temperature can be kept at any level from about 15°C to about 50°C with an accuracy of ± 0.1°C. The humidity, gaseous environment, and type and intensity of light can also be regulated.

The top and bottom ducts contain cameras, colony pickers, inoculators, spraying devices and other devices. At two points in the circulation of the trays, large picture windows are provided in order that progress of the experiment can be observed. There are also four portable magazines provided which can transport full stacks of trays to warm or cold rooms for further incubation or cold-storage pending the next step in the operation.

Ancillary equipment to the Dumbwaiter itself includes four constant temperature rooms that can operate between 0 and 50°C, an agar-making plant with a 400 liter capacity for filling the trays, and facilities for putting a large number of different agars in different trays. Three small computers control the operations of the machine and the associated tray-washing facility. One large size computer (PDP-KL 10 with 256,000 words of fast-core memory) analyzes photographs and directs colony-picking and other subsequent operations.

The system is programmed to find and count all the colonies, to measure their diameters, and to characterize their visual appearance.

The perfection of this mass cell screening technique is of major significance to the biomedical research community. Investigations of diseases of abnormal cell growth, such as cancer, birth defects, and some virus disease have been difficult and slow because the abnormalities in cell growth are commonly unpredictable and infrequent. Rates of mutation alone may be of the order of one in a million cell multiplication events.

(more)

Many such mutational and other cellular changes, including certain cancers and drug-induced birth defects, are known to result from environmental influences. The sheer magnitude of the labor of working quantitatively with many thousands of simultaneous biological events has limited progress in this field.

Because of the ability of the Glaser Dumbwaiter system to produce large numbers of colonies of cell cultures under rigidly controlled conditions (such as temperature, gaseous atmosphere, and radiation), the study of compounds suspected of causing cancer can now be greatly speeded up.

There has been strong NIH support for this facility development for over ten years. In addition to the current Division of Research Resources funding, the National Institute of General Medical Sciences supported the early phases of the project. The National Cancer Institute and the Energy Research and Development Administration are now also providing additional support for the facility.

Cell biologists throughout the country have been invited by Dr. Glaser to utilize this national resource. Mutant hunting, genetic mapping, sensitivity assays, virus assays, mutant characterization, screening possible mutagens, carcinogens and teratogens, and colony growth rate measurements are among the applications envisioned with the use of the Dumbwaiter system.

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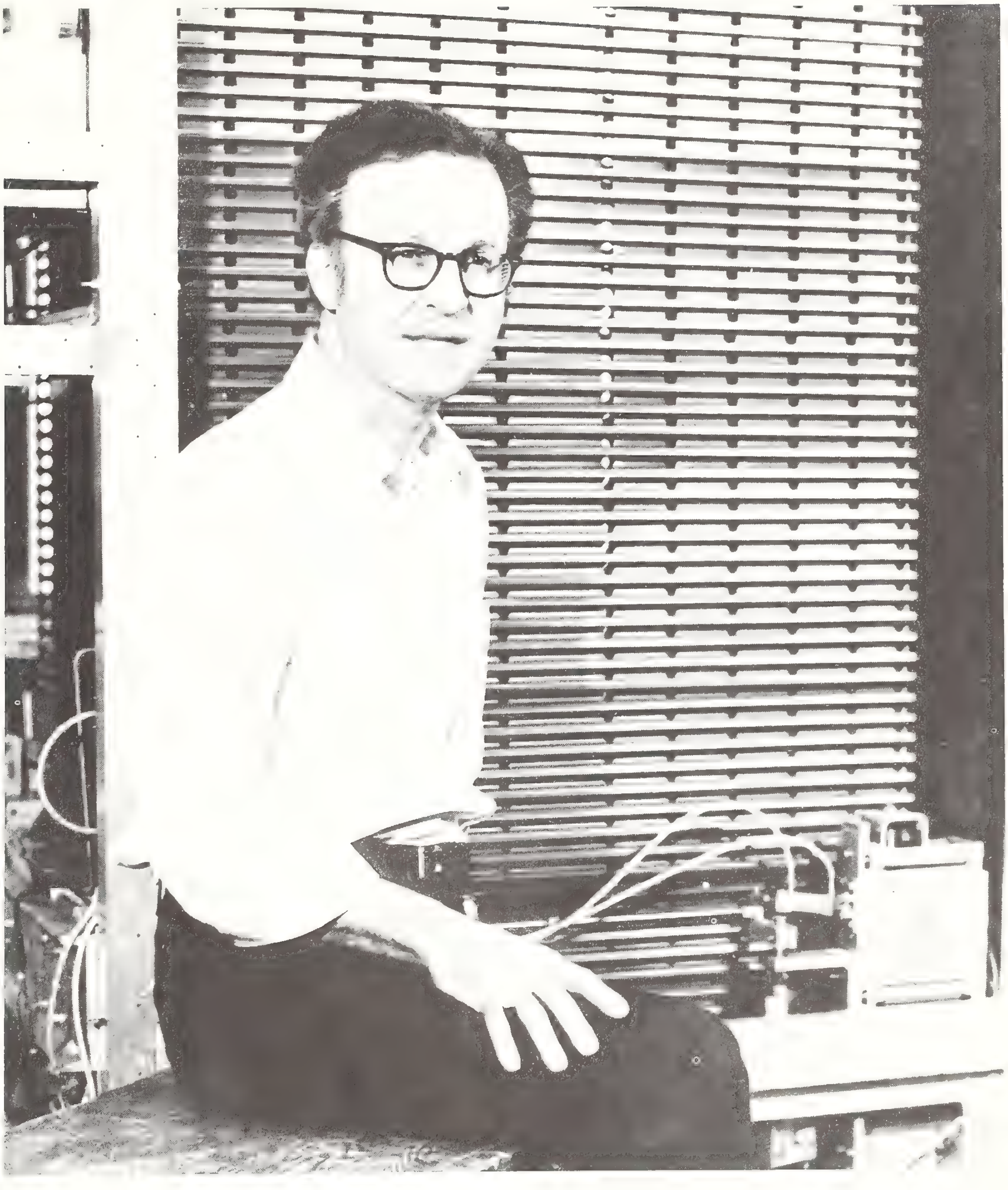
CULTURES (Cont'd)



The studies of abnormal cell growth found in cancer, birth defects, viruses, and other human diseases may be accelerated by the development of the "Glaser Dumbwaiter." The apparatus behind Nobel laureate Dr. Donald A. Glaser of the University of California, Berkeley, contains 64 aluminum trays and is part of a sterile incubator in which thousands of molecular cells may be cultured simultaneously. Supported by the NIH Division of Research Resources, the mass cell processing system is now ready for use as a national resource by cell biologists throughout the country. (NIH Photo #1552

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NEWS & FEATURES From NIH

May 25, 1976

News Feature

SCIENTISTS EVALUATE FOUR TESTS FOR "MONO"

A four-year study of a class of West Point cadets before, during, and after development of clinical and subclinical infectious mononucleosis has permitted critical evaluation of four tests used for diagnosis and research on this disease. This study, conducted by scientists from the WHO Serum Reference Bank of Yale University School of Medicine's Department of Epidemiology and Public Health, was partly supported by the National Institute of Allergy and Infectious Diseases and National Cancer Institute grants.

Infectious mononucleosis is characterized by intense formation of several types of antibody developing at different stages of the infection and persisting for times varying from weeks to years. Antibody detection, necessary to diagnose and study the disease, requires blood sample collection over an extended period and the use of the test best suited for each evaluation. In underdeveloped countries in the tropics, most children develop EBV antibodies before the age of 10, and clinical symptoms of infectious mononucleosis are almost unknown. Where socioeconomic conditions are higher, infection is often delayed, and symptoms, when they appear, are more severe. The prime susceptible population for the disease in the United States is the 15-25 year age group, the victims often being college students.

Three heterophile antibody tests -- the beef hemolysin test, the horse red blood cell test, and the sheep red blood cell test -- plus a test specific for IgM antibody to the Epstein-Barr virus (EBV) (a herpes-like virus believed to be the cause of infectious mononucleosis) were evaluated for specificity, snesitivity, and persistence of the antibody.

Of the 1,401 cadets who entered West Point in 1969 and left in 1973,

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964 arrived with EBV antibody, indicating prior clinical or subclinical infection. Of the 437 who had no EBV antibody, 53 subsequently developed the disease and another 129 developed EBV antibody without recognized mononucleosis.

Specificity, indicated by absence of EBV antibody before illness, was greatest with the beef hemolysin test. The EBV-specific IgM antibody test ranked next, the horse red blood cell test third, and the sheep red cell test a poor fourth.

In sensitivity and persistence studies of fully confirmed mononucleosis, the horse red blood cell test yielded 96 percent positive results, attained the highest geometric mean titer (1:1,906), and the antibody persisted for at least a year in 75 percent of the tested sera. The EBV-specific IgM antibody test was also highly sensitive, with 96.7 percent positive results, but titers were lower (1:14), the antibody disappeared rapidly, and the test is very difficult to perform. The beef hemolysin test yielded only 85 percent positive results, the titer was 1:152, and antibody persisted about three months, but this test, under slightly different standards would probably show better results, the scientists said.

The sheep red blood cell test performed least satisfactorily, with only 80 percent diagnostic titers, a mean titer of 1:224, and very short persistence. The scientists recommended its replacement by the horse red blood cell test for sensitivity and persistence, and the beef hemolysin test for specificity.

Drs. Alfred S. Evans, James C. Niederman, Linda C. Cenabre, Bernice West, and Virginia A. Richards, reported their findings in the November 1975 *Journal of Infectious Diseases.*

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News Feature

PROGRESS MADE IN UNDERSTANDING THE CAUSE OF CHAGAS' DISEASE

Activation of mouse white blood cells by an unrelated antigen, such as BCG, increases the ability of these cells to destroy *T. cruzi*, the parasite that causes Chagas' Disease. This finding by the National Institute of Allergy and Infectious Diseases (NIAID) and World Health Organization supported scientists demonstrates the possiblity of developing immunization procedures that would be effective in controlling some intracellular parasites.

Chagas' Disease, the American form of trypanosomiasis, causes a great amount of illness and death in Central and South American where it afflicts more than 10 million people. The chronic debilitating form of the disease, characterized by severe damage to the heart and intestinal tract, usually affects people between the ages of 15 and 50, making invalids of them during their most productive years.

White cells that ingest and destroy invading microorganisms are called macrophages. These have been found to play some role in protecting a host against parasites that multiply within the host's cells. Consequently, researchers at Albert Einstein College of Medicine decided to compare the ability of normal and activated mouse macrophages to kill *T. cruzi*. Activation, which increases the ability of cells to kill microorganisms, was accomplished by immunizing, and subsequently challenging, mice with BCG, the live organisms used in tuberculosis vaccines. The activated cells were then removed from the animals, and placed into cultures. Normal macrophages were also cultured.

When the grantees examined the cultures 24 hours after infection with *T. cruzi*, they found that the activated macrophages were more advanced in killing the parasites than the normal cells, provided the ratio of the parasites

(more)

to the macrophages was high, 10:1. (At a ratio of 1:1, there was little difference in killing between the two types of cultures.)

After four to six days, the difference in the high ratio cultures was even greater. Almost all the activated macrophages had killed and digested the intracellular parasites whereas the normal cells had allowed *T. cruzi* to grow extensively within them. Furthermore, the parasites were multiplying in the normal cell's cytoplasm or fluid rather than inside the vesicles or sacs by which they are taken into the cells and where they are susceptible to destruction by the cell's enzymes.

The researchers feel that, in man, *T. cruzi* probably survives in normal cells by escaping into the cytoplasm where there are no special mechanisms for killing the parasites. This situation has been found to exist with bacteria that cause leprosy. These findings stress the importance of the lysosomes, the structures in the cells that contain the degrading enzymes, in controlling the growth of intracellular parasites as well as the necessity for developing drugs that can act within the lysosomes.

Although BCG activation of macrophages did enhance the killing of *T. cruzi*, the New York scientists point out that nonspecific activation has not been found to increase destruction of several other parasites that causes diseases in man and animals.

The researchers, Yvonne Kress, Barry R. Bloom Murray Wittner, Adam Rowen, and H. Tanowitz, reported their study in *Nature*.

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NEWS & FEATURES From NIH

May 25, 1976

News Feature

DENTAL RESEARCHERS CONTINUE INVESTIGATION INTO SALIVA

A substance found in wheat germ can block saliva's ability to aggregate or clump together bacteria implicated in tooth decay.

The value of a group of unusual chemicals called lectins as tools to study reactions between saliva and bacteria was discussed in March 1976 at the general session of the International Association for Dental Research by Dale B. Mirth, Ph.D., of the National Institute of Dental Research.

It is well known that a marked reduction in the normal supply of saliva is generally followed by sharply increased tooth decay. It is not clear, Dr. Mirth said, whether the increase is attributable simply to less washing away of food residues and less dilution of bacterial acids, or to reactions of certain salivary substances with bacteria. According to one scientific theory, saliva by aggregating bacteria prevents them from attaching to teeth and other tissues, hence a small amount of saliva could be inadequate to cope with large numbers of bacteria. Saliva normally aggregates several strains of *Streptococcus mutans* which are implicated in dental decay.

Another theory holds that salivary aggregation of bacteria could be harmful because if may increase the film of destructive bacterial plaque that encircles teeth at the gum line. Plaque is associated with periodontal disease as well as tooth decay.

Dr. Mirth is interested in the wheat germ lectin because it reacts with saliva. "All the lectins," he says, "are found in nature, chiefly in plants. They aggregate red blood cells, certain bacteria, and various sugars. Lectins are appropriately named from the Latin *legere* meaning to select or choose because they are very choosy as to the molecule with which they will react.

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SALIVA (CONT'D)

The wheat germ lectin reacts only with cells or molecules that have a particular sugar (N-acetylglucosamine) on their surfaces. Other lectins react with different sugars such as mannose or glucose."

According to Dr. Mirth, the salivary chemicals that link bacteria into clumps large enough to precipitate are probably sugar-containing proteins (glycoproteins). But which sugar is fastened to the protein and how it functions in attaching bacteria is not well understood.

Dr. Mirth's group found that if they added the wheat germ lectin to saliva and then removed the precipitate by centrifugation, the saliva would no longer clump *S. mutans* because all the molecules of the aggregating factor in the saliva had bound to the lectin and precipitated. Then the investigators added N-acetylglucosamine to the lectin before they added the saliva. This time they found that the effect of the lectin was blocked. The excess N-acetylglucosamine occupied all of the lectin's binding sites so none was free to combine with the salivary aggregating factor.

The investigators plan to use the selectivity of different lectins as tools to study dental plaques in animals in hope of finding out more about the role of saliva in plaque and caries formation.

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News Feature

ORTHODONTIA FOR ADULTS SEEN AS A POSSIBILITY

The recent finding that the upper jaw does not completely unite with the frontal bone of the skull until people are over 70 years of age makes it possible to treat adult patients who have protrusion of the upper jaw (maxilla) and other related disfigurements. This knowlege will encourage orthodontists to use traditional appliances instead of, or in addition to, surgery for treating midface problems.

Orthodontists reshape bone and move teeth by applying direct force to teeth, and then to the supporting bone and sometimes joints. In time, pressure changes the shape of a tooth's bony socket and consequently the tooth moves to a new position. Sometimes the entire jaw should be moved to make a more harmonious face.

Vincent G. Kokich, D.D.S., and Benjamin C. Moffett, Ph.D., who received National Institute of Dental Research support at the University of Washington, Seattle, studied 61 skulls of humans aged 20 to 95 years, concentrating on the frontozygomatic sutures which lie on each side of the face where the zygomaxillary portion of the upper jaw meets the frontal bone of the skull. They examined the suture on one side by X-rays and close inspection. They compared the other side histologically, using a microscope to study stained sections of the tissues.

The investigators found that instead of fusing between the 18th and 35th years as expected, these bones did not unite until after age 70, and then only partially.

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NEWS & FEATURES From NIH

May 25, 1976

Disease Profile

NCI IS STUDYING A RARE SKIN DISEASE

Study of a rare skin disease could lead to a better scientific understanding of possible causes of cancer, which afflicts more than 650,000 Americans each year.

The disease, xeroderma pigmentosum, occurs in only one of every 250,000 persons and is characerized by extreme sensitivity to the ultraviolet portion of the sun's rays. A number of xeroderma pigmentosum patients have been studied at NIH's National Cancer Institute (NCI).

The patients usually develop freckles by the age of two. Skin exposed to sunlight becomes dry and scaly. Skin cancer is very likely. Of 15 patients examined at NCI's Dermatology Branch, 13 had developed skin cancer.

Xeroderma pigmentosum is inheritable, but can occur in offspring without ever appearing in either parent. Those with the disease must avoid sunlight as much as possible and use lotions or ointments as chemical "sun screens" to prevent accidental exposure.

Sunlight, in sufficient quantity, can cause skin cancer in some normal persons. Ultraviolet rays damage the DNA in skin cells of all persons exposed, but in most cases the damage is repaired quickly. DNA (deoxyribonucleic acid) is the hereditary material in each cell's nucleus and determines the cell's properties.

Unlike most persons, xeroderma patients are unable to repair DNA damage normally. This characteristic was reported in 1968 by Dr. James E. Cleaver of the University of California School of Medicine, San Francisco.

In Dr. Marvin Lutzner's Dermatology Branch, studies by Dr. Jay H. Robbins, Dr. Peter Burk, Dr. Kenneth Kraemer, and Dr. Alan Andrews, confirmed that most

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xeroderma pigmentosum patients are unable to repair DNA at a normal rate. They measured the ultraviolet-induced uptake of radioactively-labeled chemicals, DNA "building blocks," into cells from xeroderma pigmentosum patients, to replace damaged DNA segments, and found the rate of uptake lower than in normal cells. The NCI scientists also found one patient who had signs of the disease, while apparently performing ultraviolet-induced incorporation of DNA components normally. But Dr. Rufus Day of the NCI has shown that these cells are unable to normally repair ultraviolet-damaged adenovirus DNA and hence do have a deficiency in DNA repair.

NCI experiments in conjunction with Dr. Hayden Coon have revealed that the disease can exist in any one of five distinct forms. Scientists took skin cells from each of two patients and fused them into cells that contained the hereditary material of both patients. In several cases, these fused cells were able to repair DNA normally.

The scientists concluded that when the fused cells repair DNA normally, the patients had different forms of the disease--different genetic defects, each expressed as xeroderma pigmentosum. When the cells were fused, each patient's defective gene was masked by something supplied by a gene from the other patient.

Cells from patients of the same "complementation group" (the same genetic defect) usually had similar rates of DNA repair. The rates ranged from less than two percent in one group to as high as 50 percent in another. The repair rates did not correlate with the severity of the disease, however.

Several steps have been postulated as necessary for DNA repair. When

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ultraviolet light damages DNA, the molecule's structure--a double helix--is distorted. An enzyme recognizes the distortion and breaks the helix near the defect. Another enzyme removes the defective segment. A third assembles the parts for a replacement patch, while a final enzyme joins the patch to the remaining, undamaged DNA.

Four types of xeroderma apparently share a defect at the same step in the repair process. Experiments by Drs. Kurt W. Kohn of NCI, Albert J. Fornace, Jr., now of Peter Bent Brighan Hospital, Boston, and Herbert E. Kann, Jr., now of Emory University School of Medicine, Atlanta, indicated the defective part of the DNA was removed more slowly than normal. Although the four genetic defects were at the same stage of the repair process, they apparently involved different parts of the enzyme's structure.

The fifth form of the disease, termed "variant xeroderma pigmentosum" probably is a genetic defect that causes the DNA patch to reseal more slowly than in normal persons, Dr. Kohn's experiments showed.

The inability to repair DNA may eventually lead to skin cancer. Although the mechanism is not yet understood, it is thought that the damaged DNA somehow causes cells to change from normal to cancerous.

The same enzymatic steps that enable cells to repair ultraviolet damage also are involved in repair of damage caused by certain chemicals, including ones that cause cancer. Experiments have shown that cells from xeroderma pigmentosum patients repair chemically-induced DNA distortions more slowly than do normal cells.

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The mechanism of DNA repair might be an important step that prevents most persons from getting cancer. Dangerous environmental chemicals might cause DNA damage that most normal cells are able to repair. But in some cells, the natural protective mechanism might be overwhelmed, leading to cancerous changes.

#

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NEWS&FEATURES FROM NIH

PORTFOLIO — SKIN DISEASES

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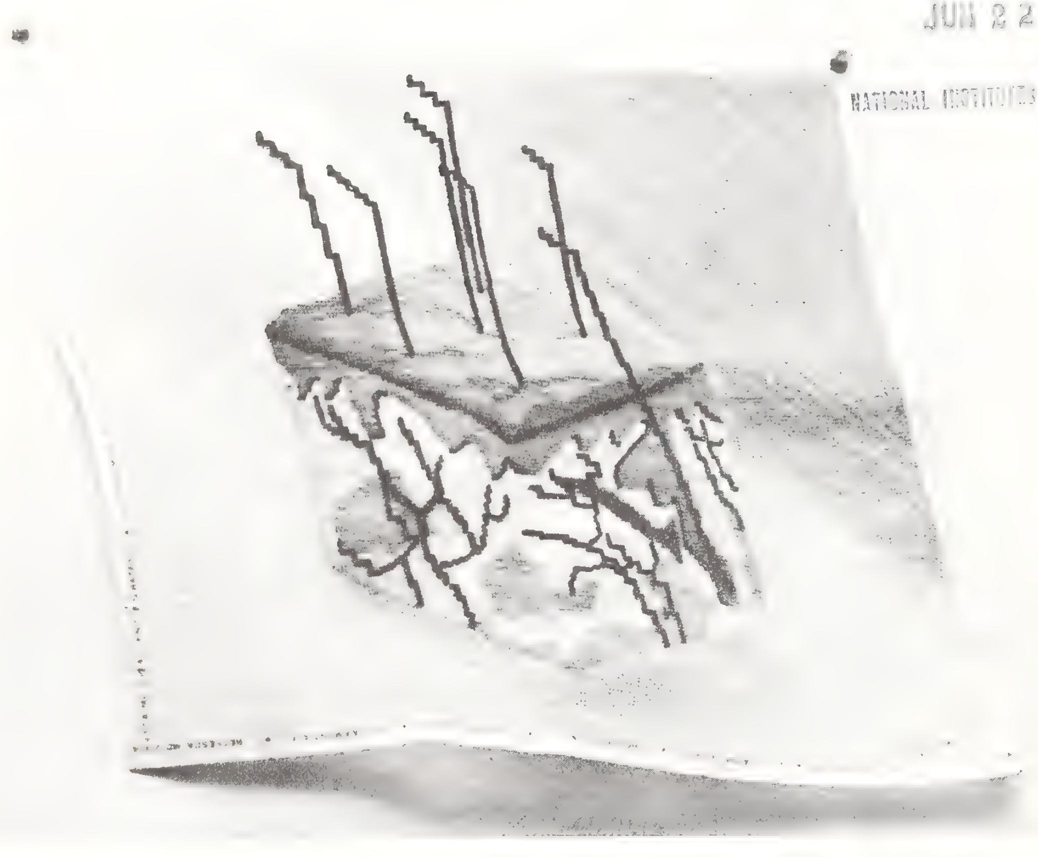

Cover Photo: Needlepoint by Leslie M. Miller depicting cross-section of human skin.

JUNE 1976

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PORTFOLIO OF SKIN DISEASES: INTRODUCTION

Federal support of basic research into diseases of the skin is provided mainly through the Extramural Programs of the National Institute of Arthritis, Metabolism, and Digestive Diseases. While a number of dermatologic diseases today are still fatal, the seriousness of most dermatologic disorders is due to the distressing visibility of their anatomical location; they can be totally disabling and disfiguring, destroying lives without actually being lethal. Because of these aspects, the medical, psychological, social and economic impacts of cutaneous diseases are considerable.

The rapid expansion of Dermatology departments in the last twenty years has been outstripped by the explosive expansion of information within that specialty and in related areas of medical research. In response to public and Congressional interest NIAMDD funding of research and research training in cutaneous biology and dermatology has likewise increased. Currently support is being provided for research in psoriasis, acne, atopic dermatitis, blistering diseases (pemphigus, phemphigoid), lupus erythematosus, pigmentary disorders (vitiligo), scleroderma and others. At a more basic level financial aid is being provided for studies in anatomy, biochemistry, physiology, histochemistry and ultrastructure of the skin and its appendages. This includes studies of the effects of aging, radiation and ultraviolet on skin, hair and nails and their structure and function, studies on the process of keratinization, sweat gland function and collagen disorders. Cutaneous microcirculation immunology and metabolism are beginning to receive more attention.

The following diseases and disease areas have been the subject of more intensive research on the part of NIAMDD-supported scientists:

Psoriasis:

Psoriasis is a disease that is both physically and socially crippling to several million Americans. Recently training grant supported scientists reported clearing of psoriasis skin lesions in a significant number of patients who were given an oral dose of a photo-active drug, methoxsalen, and were subsequently exposed to long wave ultraviolet light. Although this type of interaction of light and drug, "photochemotherapy," is not a permanent cure for psoriasis, it appears to clear the skin lesions effectively and its repeated use seems to be well tolerated by the psoriatic patients who have been treated thus far.

Currently supported NIAMDD grantees described initially the altered hormonal controls in the skin of patients suffering from psoriasis. This apparent defect in cyclic AMP enzyme regulation is being actively pursued within the context of a newly enlarged grant program. Broad ranging studies in psoriasis will combine the efforts of investigators of multiple scientific disciplines including dermatology, biochemistry, pharmacology, pharmacy and anatomy. A collaborative project at another university will be directed toward the detection of cell mediated immunity in psoriasis. An attempt will be made to formulate an in vitro model of psoriasis utilizing transplantation of normal and psoriatic skin to germ free congenitally athymic mice.

In keeping with the multipronged attack on psoriasis a contract has recently been awarded by the NIAMDD to evaluate and investigate the effectiveness on psoriasis of established cancer therapeutic agents incorporated into creams, ointments and solutions. If found to be effective, direct applications to the skin of these potent drugs would reduce the risk of the toxic side effects that frequently accompany their systemic use.

Melanin:

The cells of the skin containing the pigment melanin are responsible for giving the tiger his stripes, serve to differentiate the races of mankind and permit the chameleon to adopt his color to his environment. The importance of these melanocytes is attended to by their control from the pituitary gland. One of man's deadliest cancers, melanoma, involves these pigmented cells. Disfiguring and dangerous diseases such as vitiligo (partial loss of pigment), which has been estimated to affect between one and three percent of the total population, and albinism (complete lack of pigment) result from interference with melanin production. Grantees are examining the control mechanisms, especially the feedback circuits and genetic factors controlling pigment synthesis.

Photobiology of the Skin:

There is ample evidence that the effects of repeated exposure to ultraviolet radiation of human skin are cumulative and eventually lead to serious alterations resulting in premature "aging," cancer, and a variety of light induced diseases. In recent years, additional diseases due to drug induced photosensitivity have become a serious problem, as new chemicals are introduced into the population for general consumption.

Erythropoietic protoporphyria (EPP) is a disease marked by sensitivity to ordinary visible light. This sensitivity manifests itself as a burning sensation in the exposed skin followed by edema and erythema. Treatments successful in preventing sunburn have not been effective in controlling the photosensitivity in EPP. Research is being supported by the NIAMDD to evaluate the efficacy and safety of high doses of beta-carotene, a substance that occurs naturally in many plants and bacteria. Thus far,

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the great majority of patients treated have been able to increase by fourfold or more the time they could tolerate exposure to sunlight without discomfort. No untoward side effects have been noted in toxicity studies of the patients.

Acne:

Acne is the most common disease seen in dermatologic practice. Almost all males and approximately 80 percent of females develop acne to some degree in the second and third decades of life. NIAMDD grantees are searching for some agent or agents that will control acne vulgaris before it results in the physical and emotional scarring that could be lifelong. The basic cause of acne is unknown. Control of sebaceous gland activity through the influence of estrogens, anti-androgens, antibiotics, free fatty acid levels, and membrane receptor sites are some of the areas currently being examined by Institute grantees.

Eczema:

Approximately one-third of all patients seen by dermatologists suffer from some form of eczema. Contributions of research in immunobiology, immunochemistry and immunopathology have provided a better understanding of the allergic mechanisms of eczematous diseases. In many of these cases the skin serves as a specific target organ in a systemic immunologic disorder or furnishes the antigenic stimulus or shares in the immunologic process or allergic mechanism. Using newly developed laboratory techniques, NIAMDD grantee scientists are clarifying the role of immunity in psoriasis, atopic dermatitis (juvenile eczema), blistering diseases of the skin, lupus erythematosus and diseases that appear to demonstrate the presence of altered immune reaction.

This portfolio illustrates work being performed by some of the scientists who are conducting NIH-supported research in cutaneous biology and on specific skin disorders.

This portfolio was prepared by Laurence H. Miller, M.D., Dermatology Program Director, Extramural Programs, National Institute of Arthritis, Metabolism, and Digestive Diseases.

In their laboratory at the University of Oregon Health Sciences Center, Kirk Wuepper, M.D., and Melodie Buxman, M.D., are investigating the role a cutaneous enzyme epidermal transglutaminase may play in the formation of intermolecular cross-links between precursors involved in the formation of keratin. Fundamental knowledge of this nature is required in order to determine what enzymes may be involved in the pathogenesis of specific skin disorders. Dr. Wuepper is Associate Professor of Dermatology, and Dr. Buxman is a research fellow in Dermatology at the University of Oregon Medical School.

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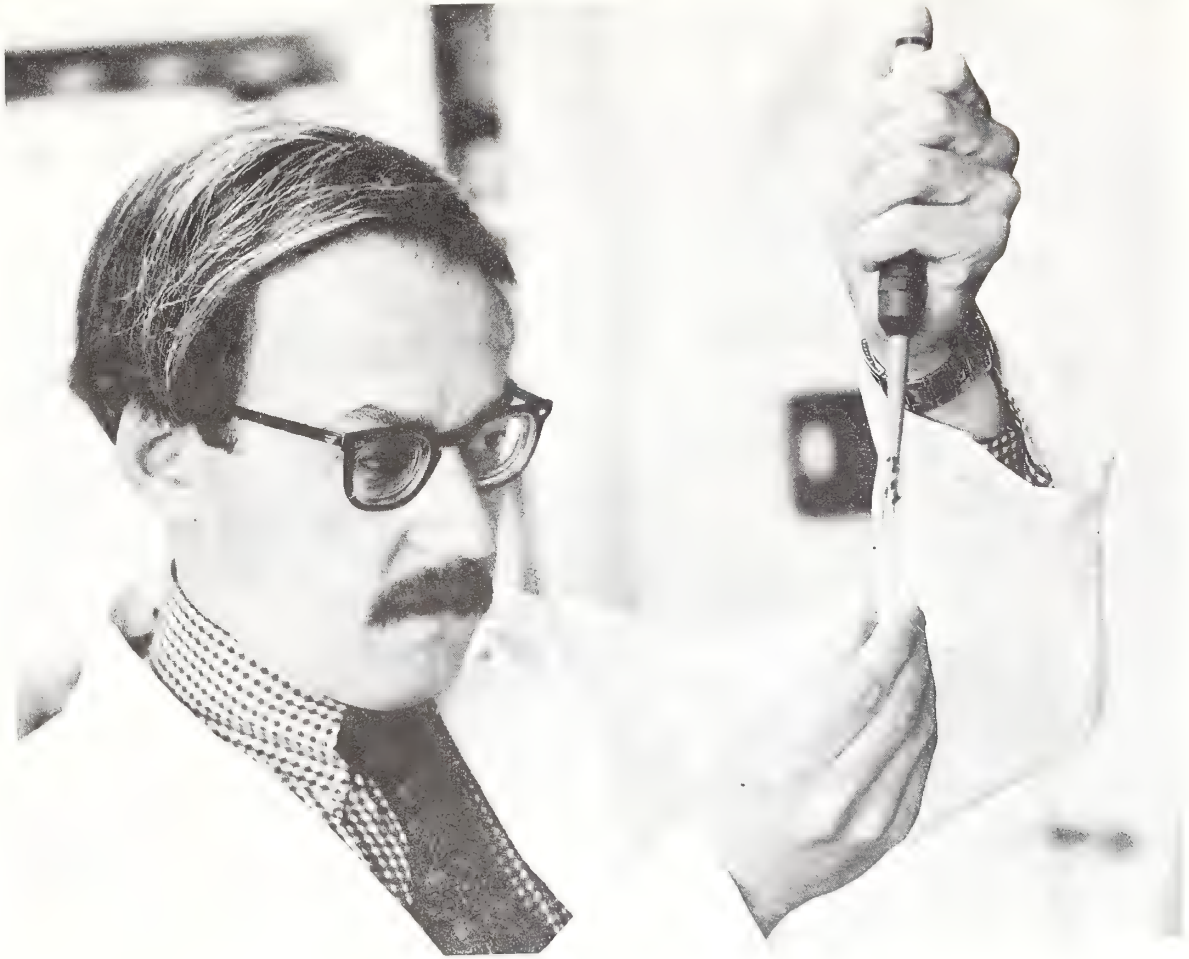
Raul Fleischmaier, M.D., Professor and Director of the Division of Dermatology at the Hahnemann Medical College, has a specialized interest in scleroderma, a disease that not only causes thickening of skin with consequent loss of mobility particularly of the hands, but can also have internal manifestations. Dr. Fleischmaier is examining the tape read-out of his scintillation counter, which is being used to determine the uptake of C^{14} *proline by scleroderma fibroblasts.*



John Voorhees, M.D., University of Michigan Chairman of Dermatology and Principal Investigator of an NIAMDD-funded research project into the biochemical etiology of psoriasis, measures cyclic AMP using an Eppendorf pipet for a Gilman cyclic AMP assay in his laboratories within the Kresge Institute at the University of Michigan. Dr. Voorhees and his co-workers were the first to describe altered hormonal controls (cyclic AMP) in the skin of patients suffering from psoriasis.

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In its progress from the basal layer toward the outer surface of the skin, the epidermal cell undergoes a programmed series of morphological and biochemical changes. Within the Department of Environmental and Industrial Health at the University of Michigan School of Public Health, I.A. Bernstein, Ph.D., and his associates Frizell Vaughan, Ph.D., (foreground and Robert Gray, Ph.D., (background) are attempting to describe such epidermal changes in molecular terms. They are particularly interested in the biogenesis of keratohyalin in the granular cells of the epidermis, elucidation of the control mechanisms involved, and definition of the aberrations in this differentiative sequence associated in conditions where there is a hyperplastic or neoplastic activity of epidermis, as in psoriasis and basal cell carcinoma respectively. Ultrastructural studies of basal cell carcinoma are being conducted in cooperation with intramural scientists at the NIH in Bethesda.

Gerald S. Lazarus, M.D., serves as Professor of Medicine and Head, Division of Dermatology, Duke University Medical Center. Dr. Lazarus and his co-workers are investigating the enzyme mechanisms involved in connective tissue breakdown and resorption in human skin. By incubating enzyme preparations with radioactively labeled materials, Dr. Lazarus has developed a sensitive method for measuring proteolytic enzyme activity. The current investigations on connective tissue enzymes are an extension of Dr. Lazarus' previous work in collagen enzyme activity in a hereditary blistering skin disease, epidermolysis bullosa.

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Marvin A. Karasek, Ph.D., is Associate Professor of Biochemistry and Research Dermatology at Stanford University. Psoriasis is one cutaneous disorder that is characterized by an unexplained increase in DNA synthesis of epidermal cells. Dr. Karasek's grant supported investigations are concerned with the metabolic control of epidermal cell growth. Studies of this type should help to provide a more precise explanation for the way nucleic acids are synthesized and metabolized in normal and pathologic skin.

The organ culture system of rat fetal skin has now been established as a reliable model for studying the differentiation of epidermis in vitro. Ruth K. Freinkel, M.D., Associate Professor of Dermatology at Northwestern University Medical School, is utilizing this system to learn more about intermediate metabolism in epidermal differentiation, particularly the synthesis of keratohyaline.

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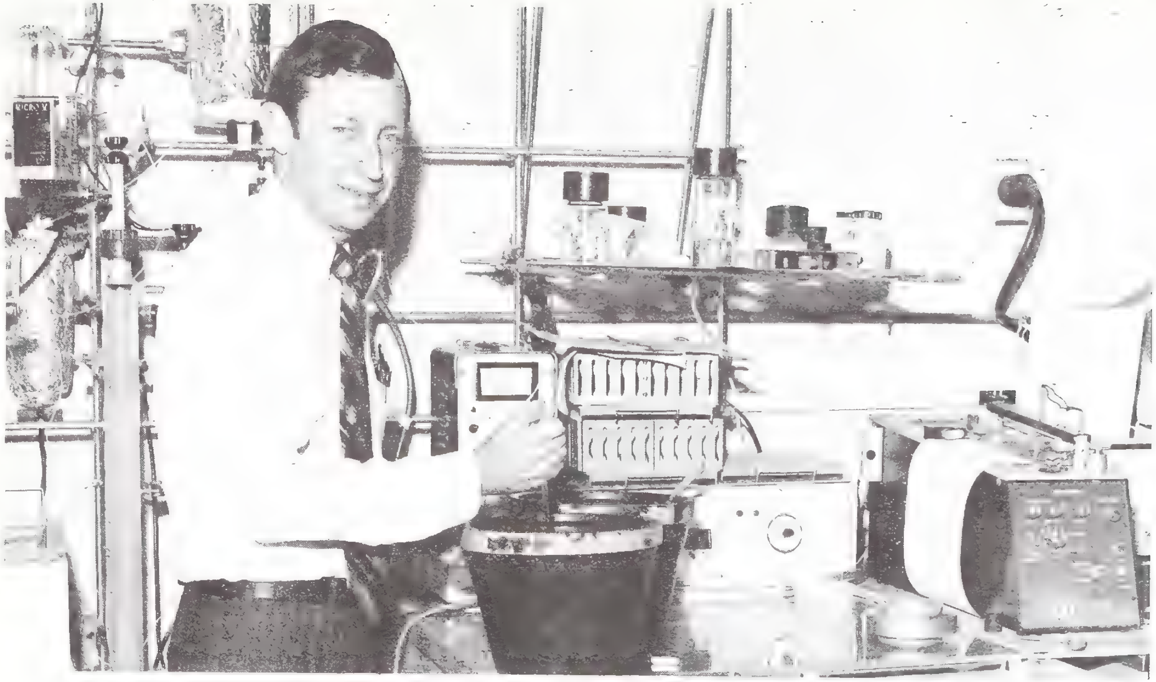

Arthur Z. Eisen, M.D., is Professor and Head of the Division of Dermatology at the Washington University School of Medicine in St. Louis. Collagen serves as the basic supporting tissue of the body. The areas of collagen metabolism under active investigation in Dr. Eisen's laboratories include the study of the localization of collagenase in human skin fibroblast cultures, the relationship of collagenase to the pathogenesis of epidermolysis bullosa, collagen turnover in psoriasis, and the regulation of collagenase production in uterus and skin. The objectives of these types of studies are to obtain a detailed understanding of the mode of action of certain human and animal collagenases and the mechanisms involved for controlling their biosynthesis and subsequent activity. This should enable investigators to gain further insight into the role not only of collagenases but other neutral proteases as well in the pathogenesis of specific skin diseases and rheumatoid arthritis, in wound healing, post-partum involution, and in the relationship of these enzymes to both cutaneous and uterine neoplasia.

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Kimie Fukuyama, M.D., Ph.D., Associate Professor of Dermatology at the University of California, San Francisco Medical Center, is involved in cytochemical studies on the keratinization process. Chemical and immunological characterization of the proteins found in cornified and granular cells in normal skin are necessary for future investigations into cutaneous pathological disorders. The microtome which is used for cutting thin tissue slices in preparation for microscopic examination is but a minor part of the large amount of equipment required to examine the biochemistry and immunochemistry of epidermal keratinization.

Kenji Adachi, M.D., Ph.D., is Associate Professor of Dermatology at the University of Miami, which has become one of the major centers of psoriasis research. In his laboratories at the Veterans Administration Hospital in Coral Gables, Dr. Adachi is studying the role of cyclic AMP in the pathogenesis of psoriasis. Utilizing only a few micrograms of microdissected psoriatic tissue, Dr. Adachi is preparing the sample for determination of phosphodiesterase levels.

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Micheline M. Mathews-Roth, M.D., is Principal Research Associate in Medicine at Harvard Medical School. Located within the laboratory of microbiology and molecular genetics, Dr. Roth has focused her efforts on the treatment of diseases aggravated by sunlight. More specifically, Dr. Mathews-Roth and her co-workers were instrumental in developing the use of beta-carotene, a natural product found in certain vegetables, as a photo-protective agent in erythropoietic protoporphyria. Prior to treatment with this agent, large numbers of patients, including many children, were unable to spend any time outdoors. The majority of patients treated with beta-carotene have improved significantly in their ability to tolerate light exposure. Support is being provided by the NIAMDD so that Dr. Roth may continue to study the efficacy and toxicity data on all patients involved in the new treatment.

In his laboratory within the Department of Dermatology at the University of Miami School of Medicine, Vincent A. Ziboh, Ph.D., is utilizing gas chromatographic assay in order to establish the biochemical basis of prostaglandin action in the skin. Evidence has accumulated that prostaglandins are involved in the pathophysiology of the skin. On the one hand, increased release of prostaglandins have been implicated as possible mediators of inflammatory reactions in the skin. Prostaglandins E and F have been recovered from skin perfusates in patients with allergic contact dermatitis, and prostaglandin-like material has also been detected in exudate from non-immune inflammatory reactions. (Recently the possible role of prostaglandins in mediating the inflammatory reactions of human sunburn have been reported.) On the other hand, decreased synthesis of prostaglandins in the skin has been associated with the development of scaly dermatoses in laboratory animals. On the basis of the increasing knowledge of prostaglandins, it should be possible soon to establish their possible therapeutic role.

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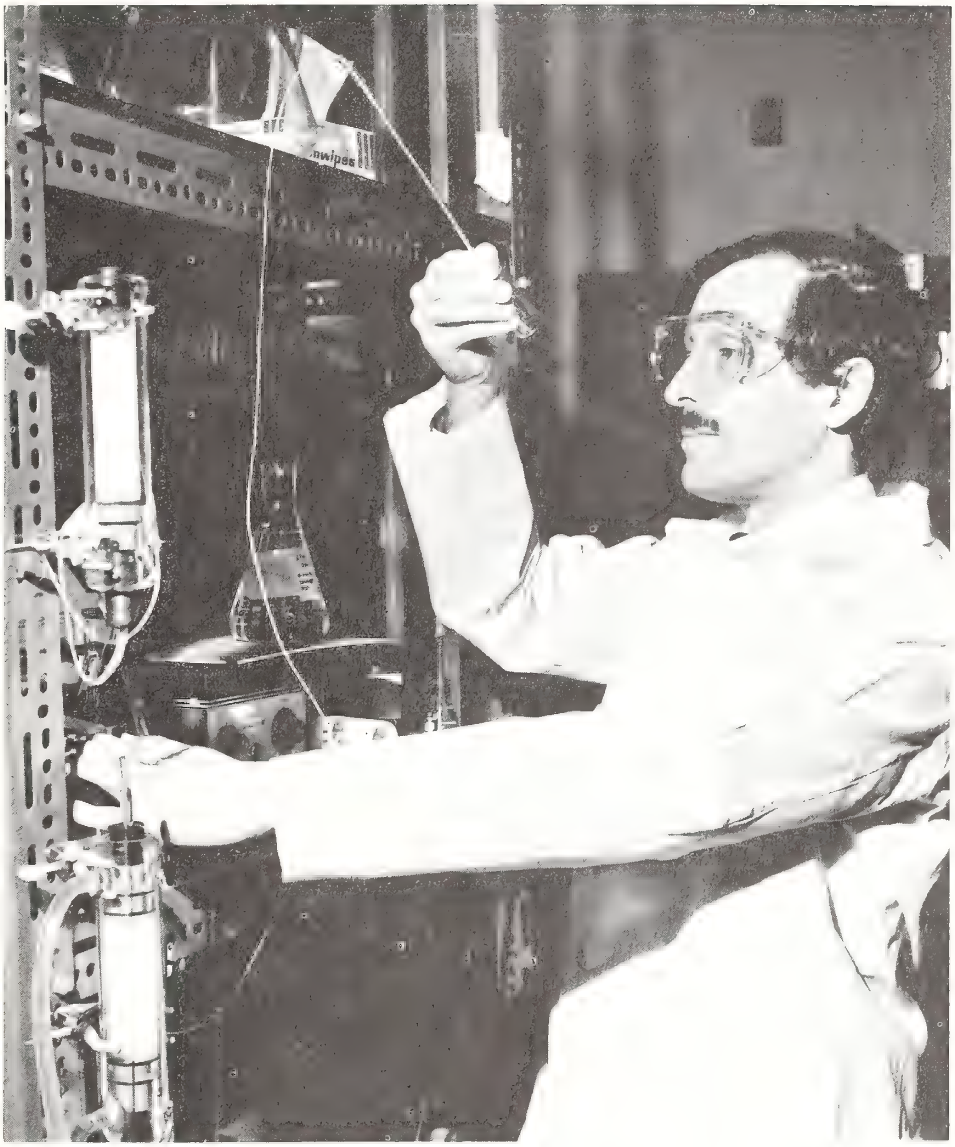
William Montagna, Ph.D., Director of the Oregon Regional Primate Research Center in Beaverton, Oregon, pursues his studies of the biology of skin of man and other primates within the Center's Division of Cutaneous Biology. Dr. Montagna serves as the principal investigator of an NIAMDD-supported research program project directed toward basic investigations of the anatomy, histology, histochemistry, physiology, and pharmacology of human and primate skin. In addition to morphologic surveys of the anatomic elements of skin, Dr. Montagna and his associates are currently looking at the genetic control of pigmentation, melanoma immunology, enzymes and metabolic patterns of animal induced melanomas, mechanisms of release and re-uptake of neural transmitters in the terminals of the autonomic nervous system of primate skin, interaction of macrophages and tumors, the effect of melanin stimulating hormone on the proliferation of keratinocytes in guinea pigs, the effect of laser irradiation on pigment cells in fish skin, and the hair of protein-deficient monkeys. It has already been established that protein deficiency in humans can be determined by analysis of hair. This primate hair study, as well as the other investigations in non-humans, provides information that can be applied to study of human disease.

The Beth Israel Hospital in Boston is one of the teaching hospitals affiliated with Harvard University. Irwin M. Freedberg, M.D., directs the Division of Dermatology at Beth Israel and is Associate Professor of Dermatology at Harvard. Dr. Freedberg's grant supported activities involve studies of epidermal macromolecular metabolism. Recently investigations have been focused on the characterization of epidermal enzymes, the ribonucleases. Once sufficient data is obtained on the ribonuclease of normal human epidermis, similar analyses of pathologic epidermis, especially that tissue obtained from clinical states with altered epidermal turnover, will be studied. This would include such diseases as ichthyosis, psoriasis, and a variety of other genetically influenced cutaneous disorders.



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Ervin H. Epstein, Jr. M.D., is Assistant Research Dermatologist and Assistant Clinical Professor of Dermatology at the University of California School of Medicine in San Francisco. Dr. Epstein's NIH supported studies began within the intramural program of the National Cancer Institute, continued at the New York University Medical Center under the auspices of an NIAMDD training grant to the Department of Dermatology, and are now being carried out in his laboratory at San Francisco General Hospital. Dr. Epstein is examining the mechanism of glucocorticoid action in human skin, both in the epidermis and the dermis, in normal and diseased skin. Although the molecular basis of steroid hormone actions has been extensively studied and to some extent elucidated in many tissues, little has been done on the actions of glucocorticoids in the skin. Such research is necessary as glucocorticoids are probably the single most commonly used topical medication for skin diseases and can exert profound effects.

Wiley M. Sams, Jr., M.D., is Professor of Dermatology at the University of North Carolina in Chapel Hill. Dr. Sams is pursuing the pathogenesis of bullous diseases. He is particularly interested in defining the mechanisms of pemphigus vulgaris, and acute or chronic disease characterized by blistering of the skin and mucous membranes. Using indirect immunofluorescent staining, other NIAMDD grantees demonstrated antibodies to the cells of the stratified epithelium in the serum of patients with pemphigus vulgaris. Although the exact mechanisms by which this disease arises are unknown, the demonstration of pemphigus antibodies have led investigators to examine more carefully the immune components of patients with this disease. Dr. Sams and his co-workers are attempting to determine if cellular immunity is playing a greater role than humoral immunity in this and other bullous diseases.

Jean-Claude Bystryn, M.D., Assistant Professor of Dermatology at New York University School of Medicine and former recipient of an NIH postdoctoral research training fellowship, is investigating several skin diseases. Dr. Bystryn's current project involves isolation of tumor antigens of human melanoma. Dr. Bystryn is injecting a mouse with partially purified mouse melanoma antigen to determine whether mice can be immunized to melanoma by this procedure.

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One of the major national and international centers of acne research is located within the Department of Dermatology at the Boston University School of Medicine. In their sebaceous physiology laboratory John S. Strauss, M.D., Professor of Dermatology, examines with his research associates, Donald T. Downing, Ph.D., Research Professor of Dermatology, and Peter E. Pochi, M.D., Associate Professor of Dermatology, a printout of a gas chromatograph which analyzes skin lipids.

For more information on this subject and for copies of photographs in this Portfolio, please contact:

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July 25, 1976

Cancer clue? See page 25

RESEARCH ADVANCES:

New Treatment Helps Prevent Formation of Kidney Stones..1
Scientists Learning Why Human Mother Does Not Reject Fetus.......................4
NIAID Scientist Adds New Details to Study of Fungus..6
New Information Gained on Lymphocyte Metabolism.......9
Methotrexate Levels in Blood May Help Predict Side Effects..11
Quick Test Shows Percentage of Living Bacteria in Plaque....13
New Test Detects Phenols in Tissues...........................15

NEWS AND PHOTO FEATURES:

New Tubeless Device Collects Parotid Saliva.................17
Simple Test Aids Cancer Cell Detection........................20
Left Atrium Enlargement May Lead to Atrial Fibrillation.....22
Scientists Study Ear Wax While Seeking Cancer Clue..........25
NIAID Grantees Have Corrected Severe Combined Immunodeficiency......................................27
Low Lactase Activity May Appear at Age Five.................29

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NEWS & FEATURES From NIH

July 25, 1976

Research Advances

NEW TREATMENT HELPS PREVENT FORMATION OF KIDNEY STONES

Researchers at the University of California, San Francisco, SF General Hospital have discovered a treatment that helps prevent formation of kidney stones in patients with certain gastrointestinal, pancreatic and liver disorders. The treatment was developed after some patients with these conditions were shown to have hyperoxaluria and oxalate kidney stones, a disorder known by the term enteric hyperoxaluria.

Results of the research were presented at the Annual Meeting of the American Gastroenterological Association on May 25, 1976. The principal investigator of the study, "Treatment of Enteric Hyperoxaluria with Calcium and Aluminum", is David L. Earnest, M.D., Assistant Professor of Medicine, UC-San Francisco. Co-investigators are William Admirand, M.D., UCSF Professor of Medicine, and Steven Gancher. Hibbard E. Williams, M.D., UCSF Vice Chairman and Professor of Medicine and Chief of the SFGH Medical Service, also collaborated in the study. The team is now preparing a report of additional findings.

In recent years many patients with gastrointestinal disease and enteric hyperoxaluria have been seen in the UCSF Clinical Study Center at SF General Hospital, a special inpatient metabolic unit founded by the General Clinical Research Center, Division of Research Resources, National Institutes of Health. This unit specializes in the study, diagnosis and treatment of little-understood disorders.

Enteric hyperoxaluria is a recently recognized entity that results from absorption of abnormal amounts of oxalate from the diet. Although oxalate is present in many foods, normally it is poorly absorbed and little of it enters

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the body. The reason for this is that oxalate binds with calcium and precipitates from solution in the intestine and is excreted in the stool.

Research by the UCSF investigators has shown that a variety of diseases characterized by malabsorption of fat are also accompanied by increased absorption of oxalate. Apparently, in these patients, the increased absorption of oxalate results from excessive binding of calcium in the intestine by the non-absorbed fat. This causes reduction of the calcium concentration in intestinal solution, which increases the solubility of oxalate and thereby its absorption by the intestine. The absorbed oxalate is then excreted in urine from the kidneys, however, if enough is present, kidney stones may form.

Enteric hyperoxyluria was first detected at SF General in patients who developed fat malabsorption after surgical removal of an extensive amount of diseased small intestine. Because it was difficult to control the fat malabsorption, it was also difficult to reduce oxalate absorption and hyperoxaluria.

"We developed the theory," said Dr. Earnest, "that if we administered fairly large amounts of calcium orally to these patients, we could provide enough calcium in the intestine to combine with oxalate as well as fat in a form that would be excreted in stool rather than absorbed and excreted through the kidneys.

"This theory was tested in 16 patients with enteric hyperoxaluria who also, for two weeks, received a diet containing normal amounts of fat and oxalate. The amount of oxalate excreted in urine was significantly less during the period when calcium was added to the diet. Moreover, as we anticipated, essentially all of the supplemental calcium was excreted in the stool.

"We also found that other compounds, such as lanthanum, zinc, barium and

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aluminum, have a similar effect in removing oxalate from solution in the intestine. We have treated a few hyperoxaluric patients with aluminum-containing compounds and have observed a beneficial effect."

"Although this treatment needs further testing," according to Dr. Earnest, "the studies have helped unravel some of the mystery behind why these patients develop kidney stones and may point the way to a simple method of preventing them in the future."

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Research Advances

SCIENTISTS LEARNING WHY HUMAN MOTHER DOES NOT REJECT FETUS

A newborn baby's T lymphocytes--thymus-derived white blood cells--suppress the ability of its mother's lymphocytes to divide. Since these maternal lymphocytes are potentially harmful, this finding by scientists funded by the National Institute of Allergy and Infectious Diseases (NIAID) may help explain why a fetus is not ordinarily rejected by its mother.

It has long been recognized that during pregnancy a mother's immune system does not respond to the foreign antigens which the fetus inherits from its father. However, the mechanisms involved in this highly successful form of natural transplantation have not been understood. Such knowledge could find application in organ transplantation where rejection of foreign tissue is the major problem.

Researchers involved in the present study, Lars Olding and Michael Oldstone of the Scripps Clinic and Research Foundation in La Jolla, Ca., had earlier shown that lymphocytes from the umbilical cords of newborns inhibited the mitosis (division) of not only their own mothers' lymphocytes but also those from unrelated adult females. As a next step, they have now separated the cord blood into populations of T cells, B cells (thymus independent cells), and macrophages to determine the specific white blood cells involved in this process.

Each cell population was mixed with equal amounts of the mother's lymphocytes. After several days, the scientists observed that in cultures which contained newborns' T cells 94 percent of the dividing cells were from the

(more)

newborns. This imbalance resulted not from overproduction of the babies' cells but from an inhibition of the mitosis of the maternal cells.

None of the many other types of cells tested could inhibit maternal cell division.

The newborns' T cells continued to proliferate while suppressing their mothers' cells, indicating that a baby's cells can resist their own inhibitory action. The scientists theorize that a newborn's cells lack the receptor upon which the inhibitory substance acts. Evidence to support this theory is the finding that T cells from one newborn cannot inhibit the cells of another newborn.

Since the newborns' T cells prevent division of cells usually associated with immune responses, Drs. Olding and Oldstone consider them to be suppressor T cells. However, they have not yet determined whether these cells have any of the other functions of suppressor T cells, such as regulation of antibody production.

The scientists reported their findings in the March, 1976 issue of the *Journal of Immunology*.

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Research Advances

NIAID SCIENTIST ADDS NEW DETAILS TO STUDY OF FUNGUS

Multiple discoveries within the past few months by Dr. Kyung Joo Kwon-Chung, a microbiologist at the National Institute of Allergy and Infectious Diseases (NIAID), have led to a new classification and to the establishment of a new genus with two species for the sexual state of the fungus *Cryptococcus neoformans*, the organism which causes cryptocococcosis. Cryptococcal meningitis is almost always fatal if untreated, and even with treatment it maintains about a 25 percent fatality rate, one of the highest for the deep fungal infections.

Dr. Kwon-Chung reported her findings, which make possible broad new genetic and epidemiologic investigations of this infectious agent, at the 76th Annual Meeting of the American Society for Microbiology in Atlantic City. She spoke at a symposium on pathogenic fungi on May 3, 1976.

The chain of discoveries by the NIAID scientist began in late 1975, when she demonstrated a sexual reproductive cycle for *C. neoformans*, previously considered to reproduce only asexually as a budding single celled yeast. By so doing, she was able to remove *C. neoformans* from the so-called "wastebasket" category of Fungi Imperfecti, and place it taxonomically with the Basidiomycetes, the classification of highly evolved fungi which includes mushrooms, as well as the smuts and rusts, which are among the major causes of disease in plants.

Dr. Kwon-Chung then went on to demonstrate that the sexual cycle involved two mating types, known as "α" (alpha) and "a". Mating permits a recombination of genes and provides a mechanism for previously impossible genetic studies,

(more)

important in determining such factors as virulence and drug resistance. As is customary when basic new discoveries of this nature are made on a fungus, Dr. Kwon-Chung renamed the sexual state of *C. neoformans*, establishing a new genus which she called *Filobasidiella* ("filo" for its filaments, and the diminutive ending "ella" for the tiny spore bearing structure) with the species remaining *neoformans*.

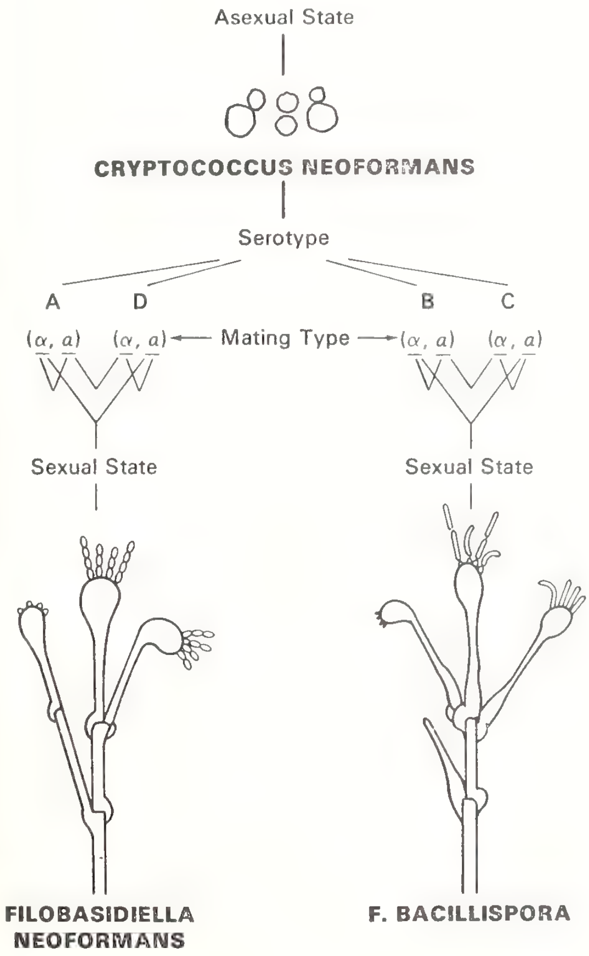
She then began to cross mate between the four known serotypes of the organism, A, B, C, and D, of which A is the most prevalent. In so doing, Dr. Kwon-Chung discovered that antigenic types A and D, found all over the world, would mate together, and types B and C (the latter causing disease mainly in California) would mate also, but that cross mating between the two groups was not successful. This finding gave a new perspective to another interesting facet of this organism. First isolated from peach juice by an Italian microbiologist in 1894, *C. neoformans*, though constantly found in human and animal infections (which are not considered to be directly transmissible), was never seen in nature again until the 1950's and, therefore, its source was never known. In 1955 the fungus was isolated from the nests and droppings of pigeons. While the birds themselves do not develop the disease, the fungus and pigeons have been closely associated for the past 20 years. In noting the distinction between mating of the two antigenic groups, however, Dr. Kwon-Chung also noted that serotypes A and D are constantly found in pigeon habitats, while types B and C have never been isolated from these sources.

Further studies by the NIAID scientist showed that mating among serotypes A and D led to the sexual cycle ending in the production of small round spores

(more)

seen in the organism which Dr. Kwon-Chung had named *F. neoformans*. Mating among serotypes B and C, on the other hand, led to a cycle ending in the production of rod-shaped (bacilli-shaped) spores. Though this second fungal species produces the same frequently-fatal disease state, Dr. Kwon-Chung has named it *Filobasidiella bacillispora* and established it to be distinct by serotype, by form, and by geography.

Dr. Kwon-Chung points out that two other fungi belonging to the same family as *F. neoformans* and *F. bacillispora* are found on plume grass, and she poses the hypothesis that the primary natural reservoir for the causative agent of cryptococcal meningitis may also be plants or plant material.



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Research Advances

NEW INFORMATION GAINED ON LYMPHOCYTE METABOLISM

A possible "biochemical handle on lymphocyte metabolism" with therapeutic implications for acute lymphocytic leukemia was discussed at the 67th annual meeting of the American Association for Cancer Research in Toronto, on May 8, 1976, by Dr. John F. Smyth, of the National Cancer Institute (NCI).

A new antibiotic, Coformycin, inhibits adenosine deaminase (ADA) activity, thereby preventing the conversion of adenosine--which is lymphocytotoxic--to Inosine, consequently interfering with reproduction of the lymphocytic series without effect on other blood cell types.

Dr. Smyth, a visiting fellow at NCI, found during previous investigations while at the Royal Marsden Hospital in London, that adenosine deaminase activity was increased by 23-fold in 16 acute lymphocytic leukemia patients over the mean ADA activity in 13 healthy controls.

This is in contrast to the situation observed in some cases of Combined Immunodeficiency Disease (CID), in which there are no lymphocytes and a genetic absence of ADA. Other studies showed that the complete absence of lymphocytes was not the cause, but possibly an effect of the low ADA titer in CID patients.

Reasoning along these lines, interference with ADA activity could cause selective lymphocytotoxicity.

Tissue culture studies involving murine leukemic L1210 and L5178Y lines and mitogen-stimulated human lymphocytes in tissue culture showed that these cells also had high ADA activity.

In vitro exposure of the two murine cell lines to adenosine demonstrated

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that concentrations of adenosine above 10^{-5}M inhibited cell division, with the toxic effect inversely proportional to the intracellular ADA activity, reported Dr. Smyth.

Interference with ADA activity to break down adenosine using Coformycin in the tissue culture systems resulted in arrest of reproduction of the lymphocytes. Inhibition by doses of Coformycin as low as 10^{-8}M produced a five-fold increase in the toxicity of 10^{-4}M adenosine to the lymphocytes and potentiated adenosine-induced inhibition of ^{3}H-thymidine incorporation into mitogen-stimulated lymphocytes.

Coformycin inhibited DNA synthesis in Phytohemagglutinin-stimulated lymphocytes by a factor of 95 to 99 percent when given in doses as low as 10^{-6} to 10^{-8}M, without the addition of any extraneous adenosine.

NCI investigators are currently working to synthesize Coformycin so that it can be used in expanded animal trials and toxicity studies. The structure of the drug, developed in Japan, is known but it is not readily produced.

Thus far, the substance is the "most powerful inhibitor of adenosine deaminase yet discovered," according to Dr. Smyth.

Potential for use is as an immunosuppressant acting directly on lymphocyte production following organ transplants as well as a specific lymphocytotoxic agent against lymphocytic leukemias.

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Research Advances

METHOTREXATE LEVELS IN BLOOD MAY HELP PREDICT SIDE EFFECTS

The measurement of methotrexate levels in the blood appears to predict whether a patient will develop serious side-effects from chemotherapy, according to Dr. Ronald G. Stoller of the National Cancer Institute (NCI).

Plasma methotrexate monitors the clearance of the anticancer drug from the blood of patients who received it in extremely high doses for osteogenic sarcoma and other forms of cancer. Measurement of serum creatinine, a routine laboratory test to assess kidney function, has been used by some investigators to predict toxicity of methotrexate. This test is unreliable, Dr. Stoller said.

These findings were presented at the 12th Annual Meeting of the American Society of Clinical Oncology, Tornoto, in May 1976. The research was conducted in the NCI's Laboratory of Chemical Pharmacology.

Methotrexate is an anticancer drug that has been commercially available since 1955. It mimics one of the B vitamins and blocks an enzyme--dihydrofolate reductase--critical in the synthesis of DNA and proteins, biochemicals necessary for cell growth. In recent years, physicians have been able to greatly increase the dosage of methotrexate because an antidote (citrovorum factor) is available to "rescue" normal cells from drug destruction.

A small percentage of patients receiving high-dose methotrexate with citrovorum rescue experience a severe fall in white blood cell and platelet counts--an event that predisposes the patient to infections and bleeding. The fall in the number of blood cells typically occurs four to seven days after the drug has been given. Previous studies have suggested that toxicity is due to blockage of drug excretion by formation of methotrexate crystals in

(more)

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the kidney tubules.

Because kidney damage preceeds the fall in blood cell count, physicians have been using a greater than 50 percent rise in serum creatinine levels to predict for marrow toxicity. Unfortunately, this test failed to predict for two out of four episodes of severe bone marrow toxicity, Dr. Stoller said. In addition, it overpredicted for two patients who did not develop toxicity and would have been given additional antidote needlessly.

Altogether, 36 patients were monitored for the appearance of toxic side-effects following 133 infusions of methotrexate-citrovorum factor. Each patient had a blood test 48 hours after treatment for levels of methotrexate and creatinine. A single infusion in each of four patients resulted in a serious decrease in white blood cell and platelet counts. These were predicted by elevated serum methotrexate levels but only two were predicted by elevated serum creatinine levels. The patients were given additional citrovorum but this measure did not prevent the drop in blood cell number.

A second group of patients had moderately elevated serum methotrexate levels and were given additonal citrovorum. These patients did not have a depression in white blood cell or platelet counts. Serum creatinine levels in this group of patients were normal.

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Research Advances

QUICK TEST SHOWS PERCENTAGE OF LIVING BACTERIA IN PLAQUE

A quick test that shows the percentage of living bacteria in plaque should speed the evaluation of new agents designed to control bacteria and the diseases they cause. Many samples of dental plaque can be assayed in a short time without having to culture the microorganisms from them.

Dr. Stanley A. Robrish of the National Institute of Dental Research described the procedures for measuring very small amounts of adenosine triphosphate (ATP) in dental plaque samples at the 54th general session of the International Association for Dental Research in March 1976.

According to Dr. Robrish, a similar analysis for viable microorganisms by conventional bacteriologic methods is very time consuming for each single sample and many of the bacteria in the mouth cannot be grown without the use of highly specialized conditions. In addition, some of the bacteria found in the dental plaque cannot be grown using existing culture methods. He also commented that much of his methodology, which he has been the first to adapt for studies of dental plaque, has been used for about 10 years by oceanographic, limnologic, and sewage-treatment experts for detecting and enumerating organisms in very low concentrations or complex mixtures.

Dr. Robrish's group found that exposing samples of cells in a hot buffer solution for about a minute would extract intact ATP. The procedure worked well with monkey plaques as well as pure cultures of bacteria. To assay the amount of ATP present, the investigators used a scintillation counter to record the flashes of light which the ATP generated when exposed to a standard light-emitting system (luciferin-luciferase from firefly tails).

(more)

PLAQUE (CONT'D)

Dr. Robrish explained that all living cells contain ATP, a high-energy form of phosphorous, in direct proportion to the size of the cell mass. After death of the bacteria, enzymes in the cells quickly transform ATP by converting it to lower energy phosphates which do not react with the test system. If an independent measure of the total cell mass (DNA or protein) can be determined at the same time that the ATP is measured, it is possible to estimate the percentage of living cells by comparing the two measurements.

For comparison with the ATP determinations, DNA could be measured in pooled plaque samples as an independent measure of cell mass, however, the DNA determination is not sensitive enough for small plaque samples. The determination of ATP is sensitive enough to measure the expected number of viable bacteria in samples as low as 10 micrograms wet weight of plaque. In the cases of small plaque samples, very sensitive methods for determining protein content are being used as an independent measure of total cell mass.

Useful as he hopes this method will be, Dr. Robrish says that it will never take the place of bacterial culture because it tells nothing about the nature of the organisms or their interrelations.

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Research Advances

NEW TEST DETECTS PHENOLS IN TISSUES

Refinement of the laboratory technique known as high-pressure liquid chromatography has permitted identification of two previously unrecognized products of a well-studied cancer-causing chemical in mammalian tissues, National Cancer Institute (NCI)-supported scientists reported on May 6, 1976.

The new system dramatically reduces the time required to identify a class of benzo(a)pyrene metabolites known as phenols, and provides a convenient method for their detection in human tissues.

Drs. James K. Selkirk and Harry V. Gelboin along with Robert G. Croy reported their findings at the 67th Annual Meeting of the American Association for Cancer Research in Toronto, Ontario. Dr. Selkirk and Mr. Croy conducted the research while working with Dr. Gelboin in the Molecular Carcinogenesis Section of the NIH National Cancer Institute in Bethesda, Maryland.

Benzo(a)pyrene is a member of a class of chemicals called polycyclic aromatic hydrocarbons. It is a potent cancer-causing agent in animals, but requires activation by another chemical, an enzyme called aryl hydrocarbon hydroxylase, to produce its cancerous effects.

Aryl hydrocarbon hydroxylase is found in many organs of the body, including human liver, skin, placenta, and blood cells. Many scientists believe it to be part of a complex enzyme system linked in some way to individual susceptibilities to cancer. Some metabolites produced by this enzyme might produce cancer; others might inhibit those effects, causing cell death.

Using a new light- and air-tight system that minimizes degradation of a test chemical while permitting it to recycle for analysis, the scientists confirmed the existence of four of 12 theoretically possible phenol metabolites

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of benzo(*a*)pyrene. In addition, they reduced the time required for such an analysis from several days to less than an hour. The metabolites were produced by action of rat liver enzymes on benzo(*a*)pyrene in a laboratory system.

The new system permits the scientists to take advantage of very small differences in the solubility of the metabolites to separate the phenols. The two new metabolites had been masked by other metabolites present in larger quantity.

Previously, the scientists had reported separation of 10 synthetic phenols of benzo(*a*)pyrene, using the same experimental conditions.

The new system for laboratory analysis of phenols produced by activated benzo(*a*)pyrene in mammalian tissues may be applied to the study of other metabolites of polycyclic aromatic hydrocarbons, the scientists said.

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Photo Feature

NEW TUBELESS DEVICE COLLECTS PAROTID SALIVA

A new, disposable, tubeless device for collecting parotid saliva has been developed by investigators at the University of Alabama with funds from a National Institute of Dental Research contract.

Dr. Milton E. Schaefer has determined that saliva samples collected in this way have flow rates and protein levels comparable to those taken in the traditional tubed cups. He points out several advantages of the intraoral cup which make it especially valuable. Laboratory personnel can insert these cups and continuously collect several hundred milligrams of saliva while doing a morning's work. Especially suited for pediatric sampling, small cups enable researchers to collect saliva from three-year-old children as easily as from adults. Moreover, while saliva is being collected simultaneously from both parotid glands, the remaining saliva from other glands can be sampled from the floor of the mouth at the same time.

The device is comfortable, reliable, and easy for an assistant to insert. The plastic from which it is made can be sterilized with ethylene oxide gas. It is inexpensive enough to discard after each use. They have found no need to stimulate saliva flow in order to collect a measurable quantity, nor is a suction device required to keep the cup in position since gentle pressure on a plastic bubble produces enough negative pressure to hold it securely.

The clear bubbles are formed by drawing Mylar plastic sheets over various sizes of circular, saucer-like aluminum templates with a vacuum-former apparatus. The resultant bubbles are then sealed to flat sheets of Mylar. Finally semicircular pieces are removed from one side of each flat, bottom sheet. An investi-

(more)

SALIVA (CONT'D)

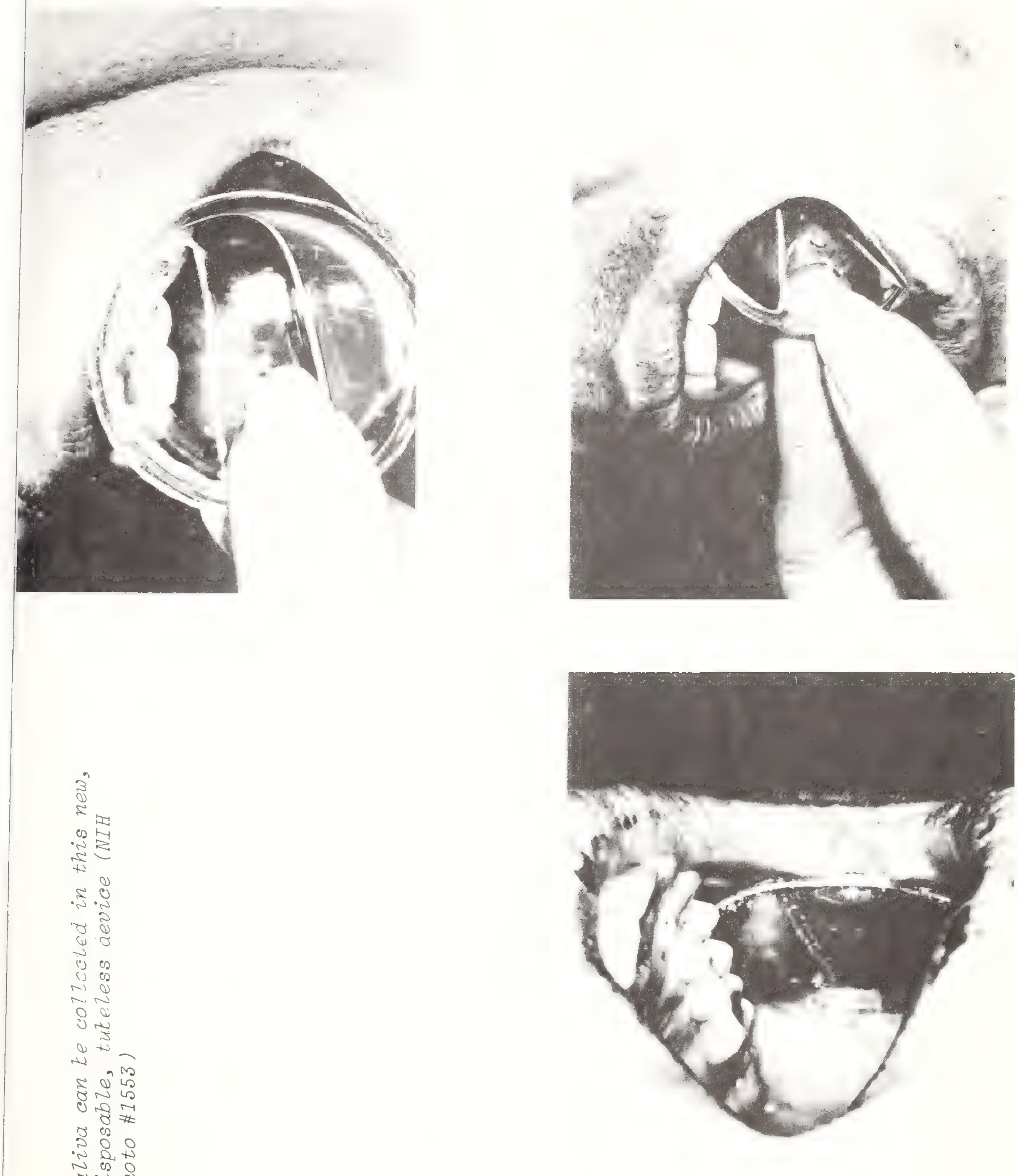
gator puts the device inside the saliva donor's cheek, carefully positioning the open semicircle over the mouth of the duct that empties from the gland. The saliva collects in the lower part of the bubble which acts as a sealed reservoir.

The investigators believe that their new device will make it possible to screen the saliva of large numbers of individuals and so detect more readily than is now done from blood samples, the small percentage who fail to make the A type of immune globulin. Immune globulins in the blood protect the body against many foreign substances, but A is the only one of them found in quantity in the mouth where protection is needed against bacteria on teeth and other tissues.

This research was reported at the March meeting of the International Association for Dental Research in Miami, in March 1976, by Milton E. Schaefer, D.D.S., Marsha Rhodes, M.S., Shirley Prince, M.T.(A.S.C.P.), Michael Cole, Ph.D., and Jerry R. McGhee, Ph.D., of the Department of Microbiology and the Institute of Dental Research, at the University of Alabama, Birmingham.

(more)

SALIVA (CONT'D)



Saliva can be collected in this new, disposable, tubeless device (NIH Photo #1553)

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News Feature

SIMPLE TEST AIDS CANCER CELL DETECTION

Research on cancer-causing agents and laboratory-grown cancer cells might be aided by a simple test studied by Dr. Robert W. Tucker of the National Cancer Institute (NCI).

The test is based on destruction of cancer cells--but not normal ones--by macrophages, white blood cells that attack and destroy "foreign" material such as bacteria in the body. Dr. Tucker described the test on May 8, 1976, at the 67th annual meeting of the American Association for Cancer Research in Toronto, Canada.

The only reliable method at present of determining whether cells grown in the laboratory are cancerous is to inject the cells into animals and wait for a tumor to develop, the NCI scientist said. Cancer cells grown in culture do not differ enough from normal cells in culture to be labeled as cancerous by any one simple test, such as microscopic examination.

Dr. Tucker found that rat, mouse, and hamster cancer cells were killed by mouse macrophages activated with BCG (bacillus calmette Guerin, a type of bacteria). The cancer cells had developed spontaneously from cell lines cultured in the laboratory for a number of generations.

The activated macrophages readily killed cancer cells but not normal cells from the same embryo. In addition, the more virulent cancer cells--those that were capable of causing a cancer rapidly in animals--were killed quicker than were cancer cells that produced cancer more slowly. The exact mechanism by which a macrophage destroys a cancer cell is not known and is the object of intense research.

(more)

CANCER (CONT'D)

Two groups of cultured cells studied in detail were not susceptible to destruction by macrophages during the period of transformation from non-cancerous to cancerous forms. Only after the rodent cells had been cancerous for 50 days would the macrophages attack and destroy them.

"For the established rodent cell lines studied here," Dr. Tucker said, "the use of BCG-activated macrophages provides a reliable method of detecting transformation of such cells in culture."

Future work will extend these studies to human cancer cells.

#

NEWS & FEATURES From NIH

July 25, 1976

News Feature

LEFT ATRIUM ENLARGEMENT MAY LEAD TO ATRIAL FIBRILLATION

Atrial fibrillation, one of the most common and important disorders of the heart rhythm, appears to result directly from chronic enlargement of the left atrium, according to echocardiographic studies in the National Heart, Lung, and Blood Institute (NHLBI). The findings are important not only for understanding what causes atrial fibrillation but also for identifying patients with normal heart rhythm who are in danger of developing it and, potentially, for preventing some of the drifting blood clots (emboli) which are a major complication of atrial fibrillation.

Drs. Walter Henry, Joel Morganroth, Alan Pearlman, Chester Clark, David Redwood, Samuel Itscowitz and Stephen Epstein of the NHLBI Cardiology Branch used echocardiography to develop a quantitative index of left atrial size in 265 patients with lesions of either of the two left heart valves or with ASH, a muscular enlargement of the wall between the two ventricles which also causes abnormal pressures inside the left atrium. They were able to demonstrate a stepwise relationship between left atrial size and atrial fibrillation. Thus, patients with left atria less than 40 millimeters in diameter generally had no atrial fibrillation, those with atria over 55 mm had chronic atrial fibrillation, and patients having occasional attacks (paroxysmal atrial fibrillation) showed intermediate left atrial sizes of 40 to 55 mm. There is also an age factor; atrial fibrillation was most common in patients over 40.

The left atrium is one of the two thin-walled upper receiving chambers of the heart. It receives the oxygenated blood from the lungs and passes it

(more)

down through the mitral valve into the highly muscular left ventricle, which pumps it out through the aortic valve to all the organs.

In atrial fibrillation, the steady coordinated cycle of atrial contraction and relaxation is lost. Instead, irregular contractions of about 400 per minute produce wormlike (fibrillary) quiverings so that effective atrial contraction is impossible. As a result, the ventricles, the heart's main pumping chambers, do not fill completely and less blood is pumped with each beat. This further loss of efficiency often contributes to heart failure. Furthermore, the formation of atrial thrombi, or blood clots, may be fostered by atrial fibrillation, posing the threat of damage to the brain (stroke) or other organs into which such clots may drift as emboli.

Based on their echocardiographic data, the working hypothesis of Dr. Henry's team is that a chronic burden of abnormal blood pressures in the left side of the heart dilates the left atrium; and it is this enlargement--perhaps partially by damaging the atrial wall--that promotes the atrial fibrillation.

They believe that it may be possible with echocardiography to identify patients at great risk of developing atrial fibrillation beforehand, then use antiarrhythmic drugs to attempt to prevent it.

There were also suggestions, in the echocardiographic study, that fibrillating patients with the greatest atrial enlargement were more resistant to routine therapeutic measures--chiefly electrical cardioversion, or D.C. countershock--aimed at reverting their heartbeat to normal. In the future, it is possible that echocardiographic identification of such resistant patients might spare them futile attempts at cardioversion and, more importantly, might

(more)

FIBRILLATION (CONT'D)

reduce the occurrence of the "post-cardioversion" emboli sometimes triggered by these measures.

Echocardiography is a burgeoning new diagnostic procedure, developed partly at NHLBI, wherein ultrasound is used to obtain visual images of the heart chambers and valves. A small transducer placed on the patient's chest generates and directs an ultrasonic beam through the chest wall at the part of the heart to be visualized. Like X-rays, waves of ultrasound pass readily through most body fluids and tissues; but a portion of the ultrasonic beam is reflected from boundaries between substances differing in density or refractive characteristics. Ultrasound beamed at the heart is thus backscattered from its surfaces and from blood-tissue interfaces within it. These echoes are electronically converted into an image of the heart that is displayed on a picture tube. Echocardiography allows exact measurements of heart structures. Completely harmless and non-invasive, it carries no risk or discomfort to the patient, even with extended and frequently repeated scans.

The NHLBI team reported these findings in the February, 1976 *Circulation*.

#

Photo Feature

SCIENTISTS STUDY EAR WAX WHILE SEEKING CANCER CLUE

United States white and black women have breast cancer mortality rates of 21 and 20 deaths per 100,000 annually, while orientals in Japan and Hong Kong have mortality rates of four and nine per 100,000. About 73 percent of Japanese women have genetically determined scant, dry ear wax; while 99 percent of American white and black women have genetically determined wet, sticky ear wax.

Medical researchers have long been aware of both these perplexing sets of statistics but Dr. Nicholas L. Petrakis of the University of California in San Francisco may have made the "apocrine" connection.

The glands which secrete ear wax and the fluid-producing glands of the breast are similar in their characteristics, both being modified sweat glands of the apocrine variety.

In studies funded by the National Cancer Institute, Dr. Petrakis evaluated the ability of women of various races to secrete breast fluid. (Women, regardless of age, whether they have ever been pregnant or nursed a baby, can secrete fluid from the apocrine ducts of the breast.) In this research, fluid was obtained by a specially-designed pump that exerts a mild vacuum, only moderately greater than that developed by nursing infants.

Over 600 female volunteers in the San Francisco area who had no evidence of breast disease served as the sample: 236 were Chinese, 225 Caucasian, 71 Mexican-American, 37 Negro, 27 Japanese and 10 Filipinos. Breast fluid was obtained successfully from 48 percent of the volunteers. Fluid samples were obtained most often from Caucasians (70 percent) and least often from

(more)

CANCER CLUE (CONT'D)

Chinese (24 percent). Chinese and Japanese women with dry ear wax had a lower percentage of successful aspirations than those with wet wax.

Having found a possible genetic link between apocrine gland function and susceptibility to cancer, Dr. Petrakis in now directing his research toward identifying cancer-causing agents in the breast fluid. Such agents, unidentified at present, may interplay with an individual's genetic make-up in the causation of breast cancer.

News Feature

NIAID GRANTEES HAVE CORRECTED SEVERE COMBINED IMMUNODEFICIENCY

Recently two groups of National Institute of Allergy and Infectious Diseases (NIAID) grantees have successfully corrected severe combined immunodeficiency disease (SCID) with injections of unrelated fetal liver cells. Although bone marrow transplantation remains the treatment of choice for infants with this rare inherited and uniformly fatal disorder, these results offer hope for those many patients without histocompatible donors.

Both groups of investigators treated their patients with intraperitoneal injections of fresh liver cells from very young human fetuses. Fetal liver, before 12 weeks, is a source of healthy stem cells that can produce lymphocytes without the fully developed ability to recognize foreignness and cause graft rejection. The procedures carried out by the NIAID grantees resulted in successful reconstitution of both T cells and B cells, the two types of lymphocytes involved in the immune response.

Drs. Richard G. Keightley, Alexander R. Lawton, Max D. Cooper, and Edmond J. Yunis, of the University of Alabama Medical Center in Birmingham, and the University of Minnesota in Minneapolis, reported their results in *Lancet*. They treated a three-month-old boy who had SCID associated with a deficiency of adenosine deaminase (ADA), an enzyme that may be related to the development of normal immunologic function. Immunocompetent T and B cells developed and the child remained free from infection for one year. He later, however, developed an ultimately fatal nephrotic syndrome.

(more)

IMMUNODEFICIENCY (CONT'D)

The most recent report was made by Drs. Rebecca H. Buckley, John K. Whisnant, Richard I. Schiff, Richard B. Gilbertsen, Andrew T. Huang, and Marvin S. Platt of Duke University School of Medicine, Durham, N.C., and Children's Hospital of Akron, Ohio. They published their results in the May 13, 1976, issue of *The New England Journal of Medicine.*

They treated two unrelated infant boys who had SCID not associated with ADA deficiency. One infant is healthy and developing normally 19 months after the operation, although he did apparently have transient graft-versus-host disease about three months after the liver cell transplantation. The other infant died of severe chronic lung disease 10 months after treatment, even though some immunologic reconstitution did occur. The differing results of these two transplants emphasizes that SCID is a complex and heterogeneous syndrome with unrecorgnized factors that may inhibit immunologic development.

Previous reports have described unsuccessful treatments with fetal thymus, which did not correct the B cell defect. Thus, fetal liver transplants, which can correct both B cell and T cell deficiencies, offer a chance of success even when a histocompatible bone marrow donor is unavailable. This treatment also offers hope to patients with other disorders such as aplastic anemia.

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July 25, 1976

News Feature

LOW LACTASE ACTIVITY
MAY APPEAR AT AGE FIVE

A Boston grantee of the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD) has measured lactase activity in morphologically normal human intestines and has determined that low lactase activity (and milk intolerance) may appear as early as five years of age in the Caucasian population.

In previous studies, Institute grantees have traced the cause of milk intolerance in adults to a deficiency in the intestinal enzyme lactase; demonstrated that this condition is very common among Negro and Oriental adults ; and described the precise mechanism by which lactose, or "milk sugar", causes the bloating, cramps, and diarrhea characteristic of milk intolerance.

The present research concerns the age at which milk (or lactose) intolerance appears in the normal human subject. In a group not characterized by significant endemic lactase deficiency--Caucasians--direct assay of intestinal mucosa for lactase activity and sucrase-to-lactase ratio has revealed a developmental pattern of two distinct groups of lactase activity. The study indicates that low lactase activity (and milk intolerance) may make its appearance in the Caucasian population at the age of five years.

Of a total of 1,077 jejunal biopsies obtained from 1967 to 1974, 172 morphologically normal ones were selected for histologic study and analysis of disaccharidase activities. Biopsies were obtained from a heterogeneous group of Caucasian patients, their siblings and parents, with an age range of six weeks to 50 years. The milk drinking habits of 118 subjects and their families were elicited, and 31 oral lactose tolerance tests were performed.

Until the age of five all biopsy specimens had high lactase activity.

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After age five, however, two separate groups emerged - 24.6 percent with low lactase activity and 75.4 percent with high lactase activity. The former group consumed little milk, showed lactose intolerance, and had low lactase activity, while the latter showed high lactase activity, normal lactose tolerance, and was characterized by a high milk consumption. The sucrase-to-lactase ratio varied accordingly.

The fact that low lactase activity appeared only after age five suggests that a high milk consumption during weaning and after may be a stimulus to prolonging lactase activity. Thus, it is proposed that while the appearance of low lactase activity in an ethnically heterogeneous group of normal individuals may be genetically determined, the time of appearance is influenced by the length and level of milk (lactose) consumption.

NIAMDD grantee Dr. Harry Shwachman of the Children's Hospital Medical Center, Boston, and associates reported their findings in *The American Journal of Clinical Nutrition.*

#

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See page 19

RESEARCH ADVANCES:

Genetic Factor Seen in Blood May Protect Against Malaria.........1
New Treatment Found for Primary Parathyroid Hyperplasia Patients....3
Elimination of Mouse Tapeworms Is Found to Be Dependent on Thymus Competence..............6
Dialysis Is Much Cheaper When Performed at Home.............8

NEWS AND PHOTO FEATURES:

Rhesus Monkey Model Is Being Developed for Asthma Studies..10
NIH Funds Resource to Study Molecules......................13
New Method Might Improve the Durability of Composite Fillings...17
NINCDS Supports Epilepsy Center in Portland Oregon.........19
Oral Vaccine Against Tooth Decay Is Tested in Animals......23

NOTE TO SCIENCE WRITERS:

The Fall-Winter Series of NIH Science Writer Seminars......27

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Research Advances

GENETIC FACTOR SEEN IN BLOOD MAY PROTECT AGAINST MALARIA

Researchers at the National Institutes of Health have identified a genetic factor found in the blood of 90 percent of the West African black population and 65 percent of the American black population which provides complete protection from infection by the most common form of human malaria, *Plasmodium vivax*. The inherited trait apparently determines the absence of two blood group antigens on the red blood cell, which is the site of the asexual malaria parasite's reproduction. The prevalence of this characteristic, known as the Duffy negative red blood cell genotype, in a population which is presently or was historically situated in a geographic location where malaria is hyperendemic strongly suggests that this alteration is the result of selective pressure following the Darwinian model.

Vivax malaria has an average incubation period of two weeks after the time of infection. Fever lasts from one to eight hours and then disappears, leaving the patient well until the next episode 48 hours later. The fever coincides with the rupturing of the red blood cells and release of parasites into the bloodstream. If left untreated, vivax malaria can subside spontaneously in ten to thirty days, but the parasites may hibernate in the liver and cause a relapse at any time over a three-year period. Although vivax malaria is rarely fatal, more than one billion people worldwide are constantly at risk of chronic infection which shortens lifespan, hinders normal growth, and retards economic development.

Dr. Louis H. Miller and his coinvestigators located 11 black and six white volunteers who had previously been exposed to the bites of vivax infected mosquitoes.

(more)

The former volunteers' blood was sampled and typed for Duffy positive or negative determinants. Three Duffy genes determine the presence or absence of Fy^a and Fy^b antigens on the surface of human red blood cells. Five of the black volunteers were both Fy^{a-} and Fy^{b-}, these same five had not been infected by the malarial mosquitoes. The remaining six black and six white volunteers were Duffy-positive, with either Fy^{a+} or Fy^{b+} antigens, or both. All twelve of these men had developed vivax after being bitten. This study supports the hypothesis that the presence of Duffy determinants, and not another closely linked factor, is the receptor for the vivax parasite.

In previous research done by Dr. Miller and his associates, they demonstrated that Duffy negative human red blood cells were resistant to invasion *in vitro* by *Plasmodium knowelsi*, a monkey malaria parasite. *P. knowelsi* was used because, up to the present, it has not been possible to grow vivax malaria in tissue culture. This laboratory research formed the basis for the subsequent blood testing and detection *in vivo* of the Duffy negative genotype providing protection against infection by vivax malaria.

Clarification of this natural resistance and the mechanism by which it works may open new approaches to the control of vivax malaria, a disease of continued global importance.

The results of this research were published in the August 5, 1976 issue of *The New England Journal of Medicine*. Coauthors with Dr. Miller were Dr. Steven J. Mason, also at the Laboratory of Parasitic Diseases, National Institute of Allergy and Infectious Diseases, Mary H. McGinnis of the NIH Clinical Center's Blood Bank, and Dr. David F. Clyde of the Louisiana State University Medical Center, New Orleans.

#

Research Advances

NEW TREATMENT FOUND FOR PRIMARY PARATHYROID HYPERPLASIA PATIENTS

Surgical research, supported in part by the National Institutes of Health's Division of Research Resources, has resulted in a new technique for the treatment of primary parathyroid hyperplasia. The new surgical procedure basically consists of the complete removal of the four parathyroid glands from their usual position in the neck and the implantation of 20 to 25 pieces of these parathyroid glands in the muscle tissue of the inner forearm.

Located behind the thyroid, the parathyroid glands are part of the endocrine system, chiefly responsible for regulating calcium, phosphorus, and bone metabolism. Primary hyperplasia (the abnormal increase in the number of normal cells) of the parathyroid results in the increased secretion of parathyroid hormone. The overactive glands raise the serum and urine levels of calcium and lower the serum level of phosphorus, while increasing its excretion.

The fatigue, nausea, and constipation at the onset of this disease rarely leads to an early diagnosis, particularly if there is a high dietary intake of calcium and phosphorus which can mask the condition. Though the incidence rate of parathyroid hyperplasia is very low, it can lead to serious complications: kidney stone formation, dysfunction, urinary tract infection; peptic ulcer; and cardiovascular disease. In chronic or acute cases bone disease may develop, evidenced by bone pain, cysts, deformities and spontaneous fracture from deossification of the bone matrix.

The standard surgical treatment for parathyroid hyperplasia is the removal of 3 1/2 glands. All too often, however, either repeat surgery is necessary to correct continued high serum level of calcium (hypercalcemia),

(more)

TREATMENT (CONT'D)

or the patient must be permanently maintained on Vitamin D and calcium supplements because the remaining half of a gland is not active enough to prevent the opposite condition, low serum calcium, or hypocalcemia.

Dr. Samuel A. Wells, Jr., of the Duke University Medical Center, and his co-investigators at Duke, Michael Reese Hospital and Medical Center in Chicago, and the University of Chicago's Pritzker School of Medicine, have departed from this approach in treating four patients with primary parathyroid hyperplasia.

Instead of leaving half of a gland remaining in the neck, all of the parathyroid glands are removed. Two of the glands are diced into 40 to 50 pieces, each approximately 1 mm. by 2 mm. (1/10" by 1/5"). 20 to 25 of these pieces are then implanted into separate beds of muscle tissue in the inner forearm. The total surface area of the parathyroid transplant, done on the less dextrous (usually left) arm, measures approximately 5 cm. by 5 cm. (2" by 2"). The remaining pieces are viably frozen in liquid nitrogen for possible future use if hypocalcemia should become chronic.

If hypercalcemia should recur, several of the implanted pieces can be removed from the forearm under local anesthesia rather than having to repeat neck surgery under total anesthesia.

Neither of these corrective techniques has been necessary in the four patients with the forearm implants. Nor was rejection of the parathyroid pieces a problem because the technique is "autotransplantation" which does not provoke the immune response which can happen when a histo-incompatible donor is involved. All four patients have normal serum calcium and phosphorus levels. Periodic measurement of the drained venous blood of the forearm

(more)

TREATMENT (CONT'D)

receiving the implant shows it to be three to 26 times higher in parathyroid hormone level than the venous blood of the other forearm, indicating a functional glandular system.

Careful long-term evaluation of the four patients is planned to assess the practicality and clinical utility of this new procedure in comparison with other established operative techniques. Future applications could include the treatment of a variety of other disease states that result in hyperparathyroidism.

The other investigators conducting this research were George J. Ellis, M.D., J. Caulie Gunnells, M.D., Arthur B. Schneider, M.D., Ph.D., and Louis M. Sherwood, M.D. Their findings were published in the July 8, 1976 issue of *The New England Journal of Medicine*.

#

Research Advances

ELIMINATION OF MOUSE TAPEWORMS IS FOUND DEPENDENT ON THYMUS COMPETENCE

Grantees of the National Institute of Allergy and Infectious Diseases have found that while normal mice infected with the tapeworm *Hymenolepsis diminuta* eliminate the worms after a 10-day growing period, congenitally thymus-deficient (nude) mice do not. This supports the concept that worm elimination by normal mice has an immunological basis and depends on competence of the thymus gland. It has been suggested that a similar concept may apply to human host with worm infestations.

H. diminuta infections usually occur in rats, where they are maintained for many months. In normal mice, following a period in which the tapeworms grow up to 16 centimeters in length, they are eliminated, so that by the fourteenth day the infection is greatly reduced, and by the twenty-first day is entirely gone. In nude mice, however, investigators at Montana State University found that prevalence of infection was high throughout a twenty-one day observation period, and the worms were frequently 50 to 70 centimeters long.

Since thymus deficiency is only one abnormality of nude mice, the investigators instituted competence by thymus grafts or injection of thymus cells. They found that nude mice so treated also eliminated the tapeworms, showing that thymus deficiency was the cause for worm retention, and thymus competence the necessary requirement for their elimination.

Recent work by other investigators indicates that nude mice do not produce immunoglobulin E and peripheral blood eosinophilia, which are often associated with parasitic infections. The authors suggest that selective

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reconstitution of nude mice with antibody of known class and activity and/or selected immunologically relevant cell types could be useful in clarifying the immunological mechanisms involved.

Dale D. Isaak, Richard H. Jacobson, and Norman D. Reed of the Department of Microbiology and the Veterinary Research Laboratory of Montana State University reported their findings in *Infection and Immunity*.

#

Research Advances

DIALYSIS IS MUCH CHEAPER WHEN PERFORMED AT HOME

Treatment costs for victims of chronic kidney disease who require periodic blood cleansing, or dialysis, are almost four times as high in the hospital as they are in the patient's own home. This, in essence, is the finding of an NIH-sponsored study of dialysis costs reported in the journal *Kidney International* and conducted in five major dialysis centers in the U.S.

The average cost of one home dialysis treatment is approximately $43, it is reported, while the average hospital treatment session costs about $159. Over the period of a year the expenditures for dialysis maintenance treatments (three per week) would amount to just under $7,000 and to $24,700, respectively, depending on the setting in which they are given.

Reporting their study results in the journal *Kidney International*, Paul A. Hoffstein and Drs. Keatha K. Krueger and Robert J. Wineman emphasized that their study was not designed to provide a statistical "average" of dialysis costs. Rather, the data are representative of the costs of a variety of dialysis modalities at several locations. As such, the data can be used to generate weekly, monthly and annual costs for any particular modality.

It was pointed out, too, that the dialysis costs reported are presented at the rates prevailing during the period of July-November 1973, when the study was conducted. Although such costs include personnel, supplies, travel, equipment and incidental expenses, they do not include physician services, radiology, and blood access surgery.

As expected, the home dialysis or self-dialysis program had decidedly the lowest cost. In such a setting, the well-trained patient essentially treats himself, although he may require some assistance from a family member. The next

(more)

most economical program is "limited care," with an average cost of $106, in which the patient is treated by nurses or technicians in a special dialysis treatment center. In third place is in-hospital dialysis. Finally, the most expensive dialysis is that performed during the initial home training phase, lasting several weeks, of a patient's home treatment program, an approximate cost of $190.

Dr. Wineman is Associate Chief of the Artificial Kidney-Chronic Uremia Program of the National Institute of Arthritis, Metabolism, and Digestive Diseases, a component of the Public Health Service's National Institutes of Health. Dr. Krueger, who was formerly associated with the same program, now is Diabetes Program Director for the same Institute. Mr. Hoffstein of the University of Texas Medical School, Houston, is President of the Nephrology Cost Group, which monitored the study, maintained uniformity and analyzed the results.

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News Feature

RHESUS MONKEY MODEL IS BEING DEVELOPED FOR ASTHMA STUDIES

A 12-monkey rhesus colony established by scientists at Northwestern University Medical School has yielded a suitable animal model for the study of human asthma. Of the colony members studied from one to three years, six were found to respond consistently and persistently with asthma-like symptoms to inhaled antigen, while five others consistently did not respond. One erratically reacting animal has been excluded from the study. Long-term immunologic, pharmacologic, and physiologic investigations are now under way.

For several years this research group, which is partly supported by the National Institute of Allergy and Infectious Diseases (NIAID), has sought a large animal model which would react in a manner and for a length of time similar to a human asthmatic.

While primates were desired as behaving most like humans, rhesus monkeys were too scarce and costly unless a very reliable response pattern could be demonstrated. Attempts to develop a dog model failed, since the animal's reactions varied too much to be useful.

In the susceptible host, swine ascaris antigen produces high levels of IgE, the immunoglobulin seen in acute human allergic reactions and found only in small amounts in non-allergic persons. All monkeys for the potential colony were, therefore, tested for cutaneous reactions to this antigen, the projected challenge material. With two control exceptions, only those with high reactivity were selected. The animals chosen were subjected to aerosol antigen challenge at intervals of two or more weeks, and respiratory

(more)

function studied. Those animals with at least six consecutive allergic respiratory responses were defined as reactors. Reactors continued to respond when challenges were withheld for periods of up to six months.

Although the responders and non-responders could not be differentiated by skin tests, by IgE concentration in serum or respiratory secretions, or by rates of leukocyte histamine release, they were distinguishable by the amount of histamine released from antigen-exposed respiratory mast cells. One theory behind asthma research is that in asthma attacks, IgE antibody which is bound to mast cells attracts and then reacts with allergens, causing the cells to release histamine and the slow-reacting substance of anaphylaxis (SRS-A). These chemicals are in turn thought to precipitate the constriction of bronchial smooth muscle and the production of excess fluid and mucus which account for the patient's distress.

The consistently responding monkeys also had a much greater reaction to an inhaled chemical--carbocholine--than did the non-responders. The authors say this could be comparable to the hyperreactivity to similar chemicals seen in human asthmatics. These cholinergic agents stimulate the nerve endings of the bronchial parasympathetic nervous system, a situation thought to occur naturally in asthmatics when emotional factors cause the nerve endings to release cholinergic chemicals, thus leading to or aggravating an asthmatic attack in progress.

Drs. Roy Patterson, Kathleen Harris, Irene Suszko, and Mary Roberts reported their findings in the March 1976 issue of the *Journal of Clinical*

(more)

Investigation. Dr. Patterson is the Director of NIAID's Asthma and Allergic Disease Center at Northwestern, one of fifteen such centers the Institute supports around the country.

#

Photo Feature

NIH FUNDS RESOURCE TO STUDY MOLECULES

A new resource that enables scientists to detect, measure, and analyze atoms or molecules with unpaired electrons has been founded by the National Institutes of Health's Division of Research Resources.

The Biotechnology Resources Program of DRR has awarded a three-year $700,000 grant to the Medical College of Wisconsin, Milwaukee, to establish a resource for Electron Spin Resonance (ESR) Spectroscopy.

Electron Spin Resonance Spectroscopy involves the study of paramagnetic components of complex systems of cells and tissues.

Paramagnetic molecules, those with free radicals (groups of atoms that enter into and go out of chemical combinations without change), and molecules containing transition metals such as iron, copper, and manganese, have unpaired electrons. Using ESR, scientists are studying the important role these electrons play in normal cellular chemistry and in the development of various diseases.

"ESR works on a principle similar to light absorption spectroscopy," said Dr. James S. Hyde, co-director of the new Center. "Instead of visible light, microwave energy is used in ESR. A sample of the matter to be investigated is placed in a strong magnetic field and irradiated with microwaves. If there are unpaired electrons in the sample, they absorb the energy and the complex electronic apparatus of this form of spectroscopy detects and measures this absorption and presents a graphic display. The spectra are then interpreted as to the amount, nature, structure, and environment of the paramagnetic molecules of the sample."

In research at the resource, scientists are gathering information on

(more)

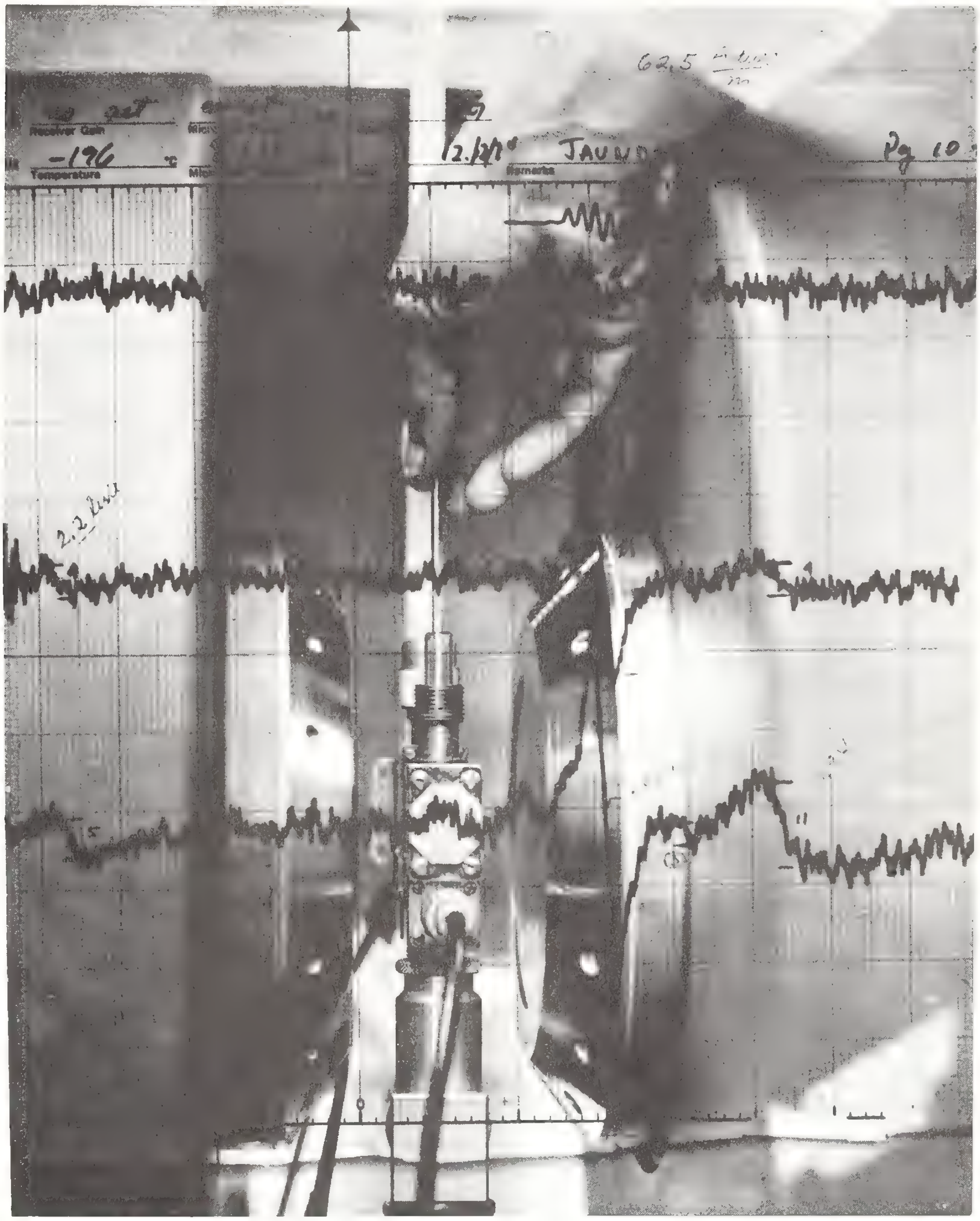
melanin, the substance in the body responsible for skin pigmentation. They have clearly identified its presence in a certain type of malignant melanoma, a form of skin cancer, called an amelanotic tumor. The identification of the tumor, in which melanin production is low, allows doctors to start appropriate therapy.

Dr. Hyde, together with Center co-director Dr. Harold Swartz, Professor of Radiology and Biochemistry at the Medical College of Wisconsin, is cooperating with basic and clinical science faculty at the institution, and with scientists throughout the nation, to use ESR to study molecular biology, cancer, organ transplantation, antiradiation drugs, and other problems.

Dr. Hyde asserts that the study of living systems with ESR is now in its infancy and that the new resource offers great opportunities for scientists to increase their understanding of the body's biochemical and biophysical processes.

(more)

MOLECULES (CONT'D)



At the new resource for Electron Spin Resonance Spectroscopy at the Medical College of Wisconsin, Milwaukee, a quartz tube containing a liver sample is placed in the strong magnetic field of the ESR spectrometer, between two circular magnets, and irradiated with microwaves. The results are shown in a graph superimposed on the machine. (NIH Photo #1554)

(more)

Drs. James S. Hyde (left) and Harold Swartz, co-directors of the new resource for Electron Spin Resonance Spectroscopy at the Medical College of Wisconsin, Milwaukee, supported by the NIH Division of Research Resources, analyze the spectra of a liver sample. (NIH Photo #1555)

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News Feature

NEW METHOD MIGHT IMPROVE THE DURABILITY OF COMPOSITE FILLINGS

The durability of composite fillings might be much improved by etching the glass particles before they are embedded in the plastic so that as the plastic hardens, its grip on the glass beads is much firmer.

A scientist working at the National Bureau of Standards in the American Dental Association Health Foundation Research Unit explained the improved process in March 1976, at the 54th general session of the International Association for Dental Research.

Dr. Rafael L. Bowen's team has been working since the 1950s, with support from the National Institute of Dental Research, to perfect the dental composite materials that he developed for filling cavities in front teeth.

Most dentists today prefer the more durable composites to the old silicate cements for restoring anterior teeth. Dr. Bowen points out that traditional gold an analgam fillings should be used in posterior teeth because they wear better under the severe grinding pressures on molar teeth. He says that composites now last about 8-10 years as fillings in anterior teeth, and they are esthetically attractive because they match tooth colors well.

Composite materials contain a resin and fillers of hard particles, usually glass or quartz. The microscopic particles add hardness to reduce wear and also make the filling expand and contract more as teeth do when the temperature changes.

Dr. Bowen explains that previously only a silane coupling agent bound the resin to the filler beads. The chemical bond between the resin and the surfaces of the filler particles was not strong enough. Eventually chewing

(more)

FILLINGS (CONT'D)

would grind off a thin layer of the softer plastic and expose a surface layer of particles. Then water and friction would loosen the particles and they would break away leaving more plastic exposed to abrasion. "We are now investigating a way to get a better bond between filler and resin," he said. "Simple as this sounds, it may have a profound effect on durability of restorations in the tooth."

The investigators have discovered that heating and cooling certain types of glass in a particular way causes a "phase separation" in which the harder silica component of glass forms a tangled network throughout the other glassy elements. Therefore, when the surfaces of the beads are etched by an acid, the softer phase dissolves first, leaving an outer layer of irregular submicroscopic channels and tunnels in the harder silica. The liquid resin penetrates these little tunnels, then polymerizes. When fully hardened, the plastic's grip on the glass beads is expected to be much stronger than it is in composites now is use.

These glasses are also clearly visible on X-ray film. Therefore dentists can easily distinguish between the filling and any secondary decay which may develop around it. Moreover, the glass is clear to light, as is the plastic, so that the composite blends well with the tooth.

Dr. Bowen notes that before the new materials are ready to market, there must be more research to learn the most efficient etching procedures.

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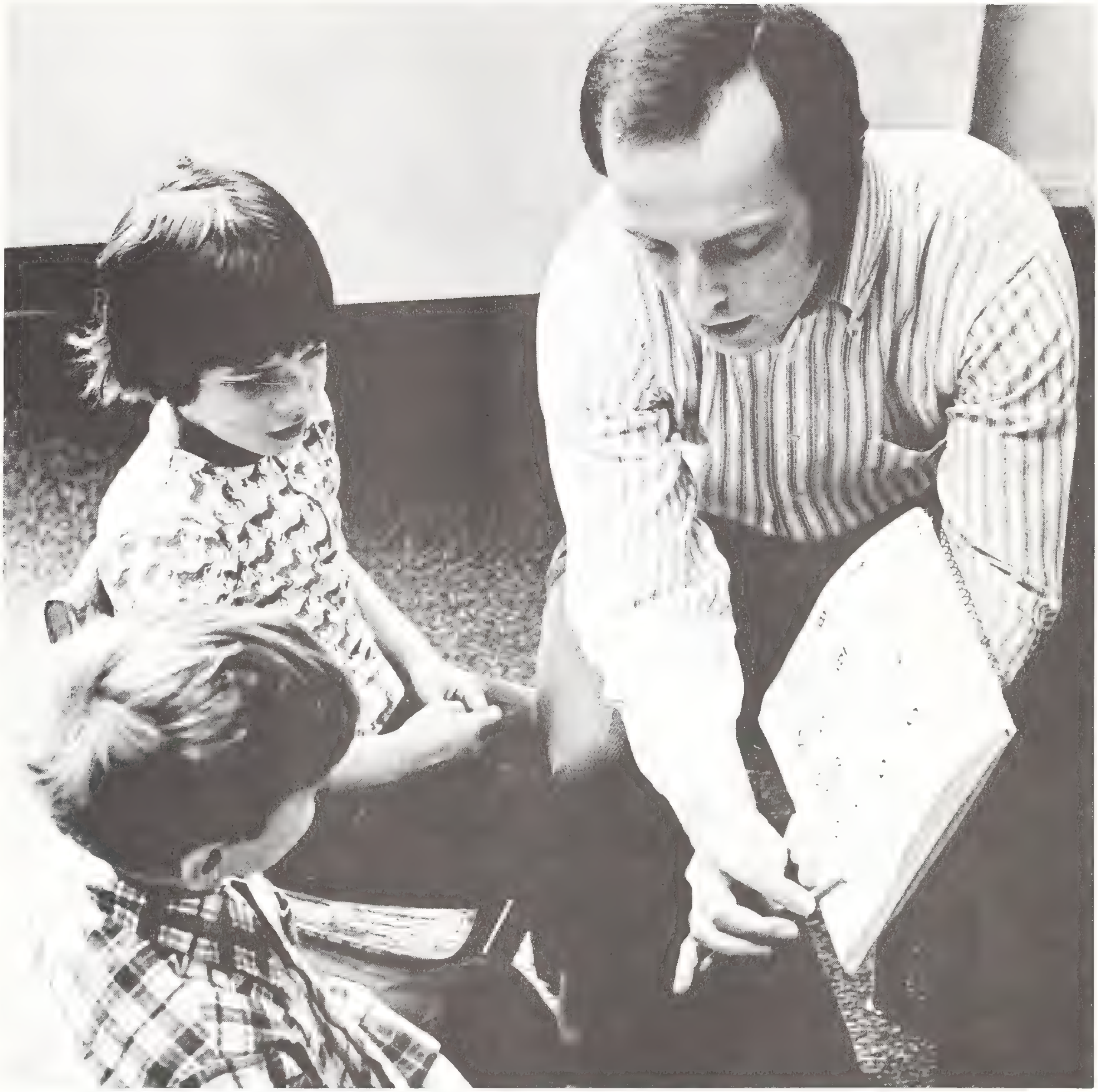
Photo Feature

NINCDS SUPPORTS EPILEPSY CENTER IN PORTLAND OREGON



Two youngsters with epilepsy sharpen their reading skills through the Distar method during a visit to the Child Neurology Clinic, a division of the Epilepsy Center of Oregon. School-age educator Patrick Highhouse chose the method becau of its high percentage of success in teaching delayed children to read. The Clinic offers diagnostic and evaluation services and prescriptive classrooms for infants through school-age children. (NIH Photo #1556)

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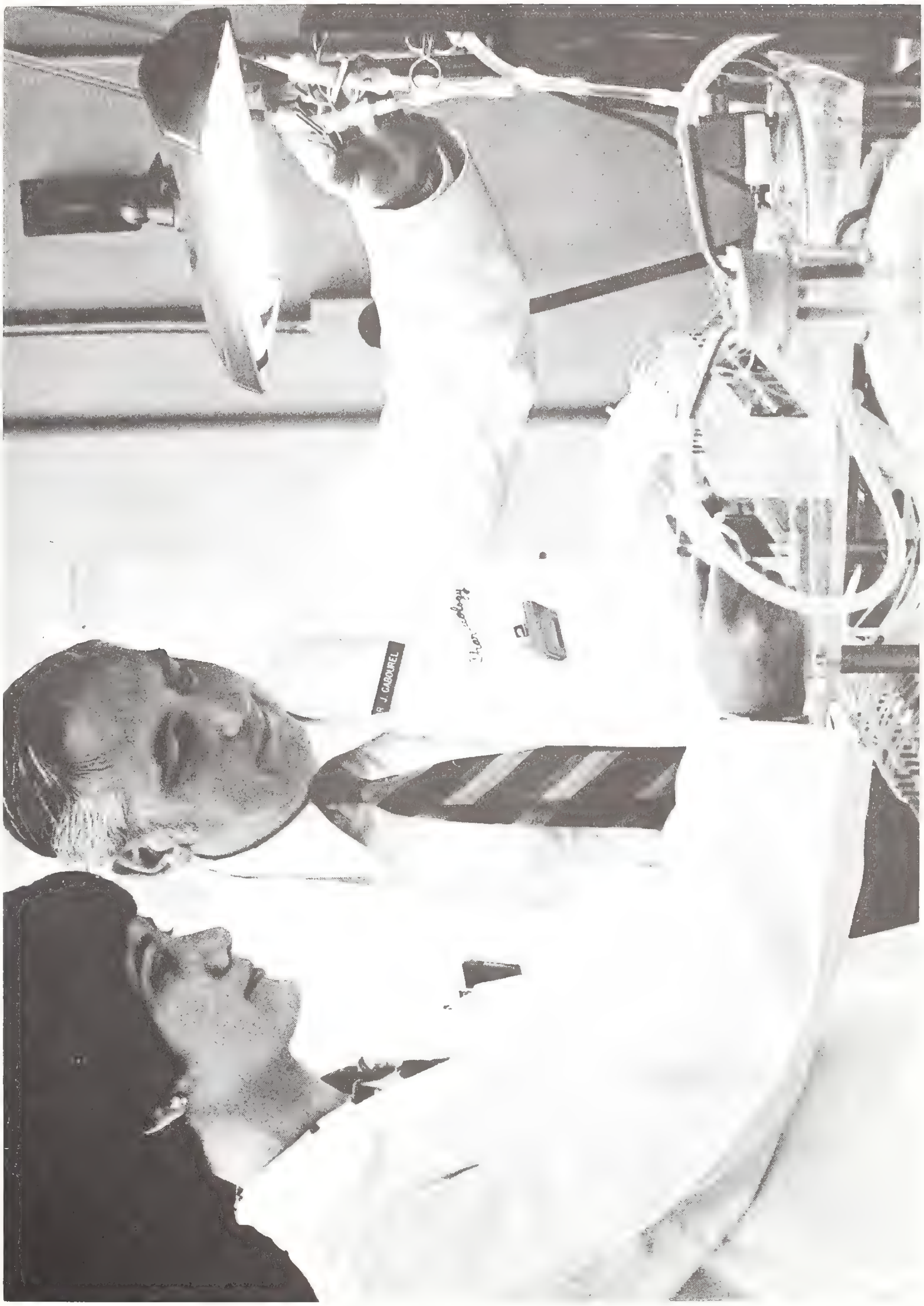
EPILEPSY (CONT'D)



Portland physician Dr. J.D. Gabourel (right) and research assistant Adriana Vasil study lymphocyte function of patients with epilepsy prior to therapy with diphenylhydantoin and after the use of the anti-convulsant drug. This research project is sponsored by the Epilepsy Center of Oregon. (NIH Photo #1557)

(more)

Neurological evaluation is an essential step in helping patients with seizures and associated problems. Such evaluation is part of the multi-disciplinary approach at the Epilepsy Center of Oregon, which also includes psychological, social and educational services. The Center is funded by a National Institute of Neurological and Communicative Diseases and Stroke contract, and seeks to develop a comprehensive epilepsy program for the state. (NIH Photo #1558)

(more)

Colorful pictures help educator Jill West teach language skills to pre-schoolers at the Child Neurology Clinic. The Clinic, a division of the Epilepsy Center of Oregon, offers diagnostic and evaluation services and prescriptive classrooms for infants through school-age children. (NIH Photo #1559)

#

NEWS & FEATURES From NIH

August 25, 1976

News Feature

ORAL VACCINE AGAINST TOOTH DECAY IS TESTED IN ANIMALS

Investigators supported by the National Institute of Dental Research at the University of Alabama have shown that by drinking a liquid vaccine rats can develop considerable protection against tooth decay.

Drs. Jerry R. McGhee and Jiri Mestecky of Alabama's Institute of Dental Research and associates in the Microbiology Department on the Birmingham campus reported these animal studies at the recent annual meeting of the International Association for Dental Research in Miami, Florida.

Young, germ-free rats were divided into two groups. Animals in the first group were given killed, decay-causing bacteria (*Streptococcus mutans*) in their drinking water. Later both groups were infected with the living organisms and fed a sugary diet. When all of the animals were three months old, samples of saliva and blood were taken, and the teeth were examined for decay. The inoculated animals had less decay on all surfaces of their teeth and much higher levels of salivary antibodies against *S. mutans* than those not consuming the vaccine.

Antibodies are immune globulin molecules which occur in the blood and other body fluids. They serve primarily to defend the body against foreign invaders such as bacteria, viruses, toxins and pollens. However, one type of antibody called secretory IgA, Dr. McGhee explains, is also found in saliva and other glandular secretions. It differs from other immune globulins in that it does not kill bacteria but makes them clump together.

Recent dental research has shown that this reaction interferes with the attachment of many bacteria to various tissues in the mouth. Prevention of attachment may explain in part how secretory IgA antibody reduces tooth decay.

Unattached bacteria are easily washed away by saliva and unable to colonize teeth long enough to make the acid that dissolves enamel. Nevertheless, this protection is not complete because some bacteria are trapped in small pits and rough places.

The production of naturally occurring antibodies in saliva, Dr. McGhee says, is thought to be stimulated by immune reactions that take place when foreign substances contact mucosal surfaces, particularly those lining the gastrointestinal tract. He believes that *S. mutans* living in the mouth (and probably other indigenous bacteria also) when swallowed can stimulate precursor lymphoid cells in that tract. These cells presumably travel via lymph ducts to local lymphoid tissue in various glands where they differentiate into the type of plasma cell which synthesizes the secretory IgA molecule.

Secretory IgA molecules are twice as large as those of serum IgA. Many immunologists have theorized that IgA, like other antibodies, was made originally in the blood. They thought that in the process of glandular excretion, two small molecules became linked. They reasoned that to stimulate salivary glands to make a particular antibody it would be necessary to inject a vaccine into or near the gland.

Last year, however, other NIDR-supported scientists showed that in proportion to their output, the hundreds of small salivary glands secreted more salivary IgA than the six large glands. Therefore, it would be hard to tell where a vaccine should be deposited to obtain the best effect. Now it appears that salivary IgA may be synthesized in salivary glands in the larger form and split by an unknown process as it progresses into the bloodstream

(more)

Interest in the naturally occurring salivary IgA molecules led the Alabama group to investigate secretory IgA in the milk of healthy females. They found that salivary antibody to the five varieties (serotypes) of *S. mutans* occurred naturally in colostrum. Moreover the antibodies reached higher levels in the colostrum than in the saliva of these individuals, and much higher levels than in their sera. This research increases the evidence that naturally occurring salivary antibody producing cells are probably not of salivary or blood origin but derive from the intestinal tract. It also increases the rationale for using an oral vaccine to attack the problem of oral infections.

Perhaps, in a few years children may swallow a vaccine to protect themselves against most tooth decay much as they now drink one for polio protection.

These findings were presented in two papers by Suzanne M. Michalek, M.S., Roland R. Arnold, Ph.D., Lorenco Bozzo, D.D.S., Jiri Mestecky, M.D., Michael Cole, B.D.S., Ph.D., Rose Kulhavey, B.S., Shirley Prince, B.S., and Jerry R. McGhee, Ph.D., of the University of Alabama, Birmingham. The research was supported by the National Institute of Dental Research.

Additional evidence in support of the theory that oral vaccines may be feasible against organisms that cause dental decay was also presented at the same meeting by Bo Krasse, D.D.S., of the University of Goteborg, Sweden, and Harold V. Jordan, Ph.D., of the Forsyth Dental Center, Boston.

These investigators swabbed the mouths of young germ-free mice and rats and of young hamsters (not germ-free) with two strains of killed *S. mutans* every day for two weeks. Some animals received dead bacteria in drinking water and food for two weeks. A week later, both treated and untreated animals were

(more)

infected with the same strains of live bacteria either applied various ways in the mouth or suspended in drinking water. Although the results were not as uniform in the hamsters as in the other germ-free rodents, fewer bacteria could usually be recovered from the immunized animals than from the controls. However, it was harder to infect conventional animals than germ-free animals, and more difficult to study their antibodies because of cross reactions with other varieties of bacteria. No method of applying the vaccine in this study proved superior to any other. How relevant these observations are for humans requires further research.

#

NEWS & FEATURES From NIH August 25, 1976

NOTE TO SCIENCE WRITERS:

You are invited to attend the Fall-Winter series of Science Writer Seminars, now in the planning stage at NIH. The Seminars, developed by the Division of Public Information and the intramural scientists of NIH, are state-of-the-art backgrounders on subjects of broad scientific interest. They are not intended to produce "hard news."

We plan to hold four or five Seminars in the 1976-77 series. All will be held on the NIH reservation in Bethesda, with the exception of the first program, which is scheduled for the National Institute on Aging's Gerontology Research Center in Baltimore, Maryland.* The date is Friday, October 1, at 10 a.m.

Host of the occasion will be Dr. Robert Butler, Director of the National Institute on Aging.

Subjects to be discussed include: the normality of aging (the Baltimore Longitudinal Study); diabetes and aging; biofeedback research; and the effect of drugs and diet on the aging.

For program details, please call Dan Rogers at (301) 396-9421.

For additional information on the entire seminar series, please call Ms. Jane Collins at (301) 496-9151, coordinator for the series.

---

*For those who need transportation, buses will be provided departing from NIH Building 31 at 9 a.m., and returning to Bethesda about 4:30 p.m. To reserve a seat on the bus, please call Ms. Ann Shalowitz, NIA Information Office at (301) 496-5597.

Editors of publications may request a glossy print of the numbered photographs that appear in this issue.

Ms. Joyce Flaherty
National Institutes of Health
Building 31, Room 2B-10
Bethesda, MD 20014

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NEWS&FEATURES FROM NIH

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NATIONAL INSTITUTES OF HEALTH

October 25, 1976

See page 4

RESEARCH ADVANCES:

NIAID Tries Vaccination Against Sexual Forms Of Malaria Parasite....1
Tadpole Is Model in Demyelination Study....4
Cells of Urticaria Patients Found to Be Defective in Releasing One Chemical..........8
Cause Sought for Hypergonadism in Some Malnourished Males..10
Special Fast Tried for Adult-Onset Diabetics..............12

NEWS AND PHOTO FEATURES:

Dr. Gajdusek Is Shown in 1956 and 1976......................14
Tourette's Syndrome Is the Cursing Sickness...............15
New Instrument Helps Speech Scientists Compare Findings....19
Careful Tests Planned for New Drug to Dissolve Gallstones..20
Certain Thyroid X-Irradiation Is Possible Cause of Tumors..24
PHS Announces National Immunization Conference............27
NIH Issues Some Documents Related to DNA Guidelines.......29

NOTE TO SCIENCE WRITERS:

Seminar on Cardiovascular Diseases........................30

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October 25, 1976

Research Advances

NIAID TRIES VACCINATION AGAINST SEXUAL FORMS OF MALARIA PARASITE

Scientists at NIH's National Institute of Allergy and Infectious Diseases have taken a new approach to controlling the spread of malaria -- vaccination against the sexual forms of the parasite that infect the mosquito. By inducing this immunity in chickens on which the mosquitoes feed, they have blocked the parasite's development in the mosquito, thus preventing it from transmitting the disease to its next victim.

Attempts by other investigators to produce an anti-malarial vaccine have been directed against the parasite's asexual forms when they are outside the infected host's cells as free parasites, and probably most vulnerable to defense mechanisms such as antibodies. The new vaccine is also aimed at free parasites, but at the sexual forms (gametes), that are released from ingested red blood cells in the mosquito's gut.

Dr. Robert Gwadz of NIAID's Laboratory of Parasitic Diseases immunized chickens for various lengths of time with red blood cells containing the avian malaria parasite, *Plasmidium gallinaceum*. These parasites had been previously inactivated by X-rays or chemical treatment.

A short time after the last inoculation, Dr. Gwadz infected the chickens with malaria. Although the vaccine had little effect on malaria infections in the chickens, the parasitic infection in mosquitoes fed on immunized chickens was significantly altered. These mosquitoes had 95-98 percent fewer oocysts -- the form of the parasite that develops in the wall of the mosquito's gut following gamete fertilization -- than mosquitoes fed on non-vaccinated chickens.

Dr. Gwadz reported his research in the September 17, 1976 issue of *Science*.

(more)

Using a different immunizing agent, Drs. Richard Carter and David Chen, also of the Laboratory of Parasitic Diseases, reduced oocyst formation even further -- 99.9-100 percent, by immunizing chickens with X-irradiated, partially purified, free gametes. All the chickens, except those vaccinated with the fewest number of gametes, remained totally uninfective to mosquitoes throughout the time when the parasites were present in the red blood cells. These results were reported in September 2, 1976 issue of *Nature*.

Further experiments by Drs. Gwadz, Carter, and Chen indicate that the protection of the mosquitoes is due to the action of antibodies that were produced in the chicken. When the mosquito ingests these antibodies along with parasites in a blood meal, the antibodies immobilize the male gametes in the mosquito's gut, preventing the fertilization of the females and the establishment of infection.

The researchers feel that the translation of a gamete-based vaccine into a realistic measure for combating human malaria faces many problems. Not only must the effectiveness of the gamete vaccine for human malarias be demonstrated, but the means must be found for producing large quantities of suitable immunizing materials. If these and other scientific problems can be overcome, gamete vaccination may have considerable significance not only for the control of malaria, but possibly for other vector-borne diseases -- such as trypanosomiasis and filariasis -- in which the disease organisms undergo marked transormations after entry into the vector.

(more)

MALARIA (CONT'D)

Dr. Robert Gwadz (left) and Dr. Richard Carter (above) prepare the Long Island Red chickens. The infectious mosquitoes, are contained in the white cups with a fine screen top. The cups are taped in place with the screen side down, allowing the mosquitoes to feed but not escape. (NIH Photo # 1563 and 1564)

#

TADPOLE IS MODEL IN DEMYELINATION STUDY

A tadpole with a transparent optic nerve is providing a new and direct look at the destruction of the protective covering of nerves, called "myelin", by cerebrospinal fluid from multiple sclerosis patients.

Demyelination is considered a primary sign of multiple sclerosis (MS), and long has been thought to be at least partially responsible for the various symptoms of MS, including disturbances in vision, muscle strength, and mobility.

Dr. Henry Webster and his colleagues at NIH's National Institute of Neurological and Communicative Disorders and Stroke (NINCDS), who developed this Xenopus tadpole model, have found that cerebrospinal fluid injected into the tissue surrounding the tadpole's optic nerve diffuses quickly and penetrates into the optic nerve. The researchers can then fix the nerve and examine it with a differential interference microscope to identify and count the myelin lesions.

This model, which represents the first *in vivo* system for observing demyelinating activity, may be of additional interest because the optic nerve is frequently affected early in the course of MS, producing transitory "blind spots" in the center of vision.

The scientists also examined peripheral nerves located near the optic nerve and found that the myelin was not damaged by cerebrospinal fluid from MS patients, suggesting that whatever causes myelin destruction is aimed specifically against nerves in the central nervous system (brain and spinal cord). Since myelinotoxicity has been found by the scientists to decrease if the cerebrospinal fluid is heated, they consider this to be additional

(more)

evidence that the myelinotoxic factors are indeed located within the fluid.

Other demyelination studies have been done in tissue culture by various scientists around the world. In these other studies, however, a concentrated "pool" of fluid from many patients is required before myelinotoxicity is observed. Only 0.5 ml. (1/60 oz.) of cerebrospinal fluid is needed for a tadpole test.

The researchers' initial studies involved 46 patients, including those with MS, some with a disorder of the optic nerve (called acute idiopathic optic neuritis) and control patients having other neurological disorders.

Initially their results have shown that myelinotoxicity correlates closely with severity and duration of MS. It does not seem to be associated with levels of gamma-globulin or total protein, both of which are often elevated in patients with MS.

In addition, Dr. Webster and his colleagues found that myelinotoxicity (measured in number of lesions) reached maximum levels two days after infection, and became lower thereafter, indicating that the lesions were reversible and damaged areas could recover. Moreover they found that lesions produced by MS compared to those produced by other neurological disorders differed only in number but not in kind; MS cerebrospinal fluid tended to produce more lesions.

Finally, they found that this method was not useful in diagnosing MS. This is based on the observation that fluid from participants with "possible MS" who showed clinically suggestive symptoms of the disorder did not cause demyelination. Yet fluid taken from one of these participants a year later, after the disease had progressed, did cause myelinotoxicity.

(more)

TADPOLE (CONT'D)

It is hoped that eventually this tadpole model will help scientists identify just what in the cerebrospinal fluid does cause demyelination. Once this is known, researchers may then be able to develop methods to prevent and possibly find the cause of multiple sclerosis.

This research was reported in the September 16, 1976 issue of the *New England Journal of Medicine.*

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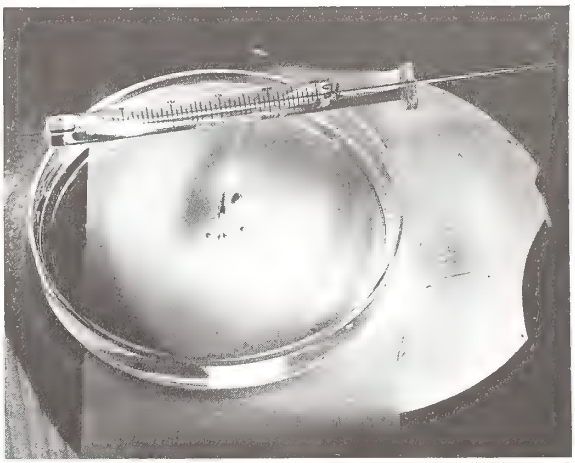
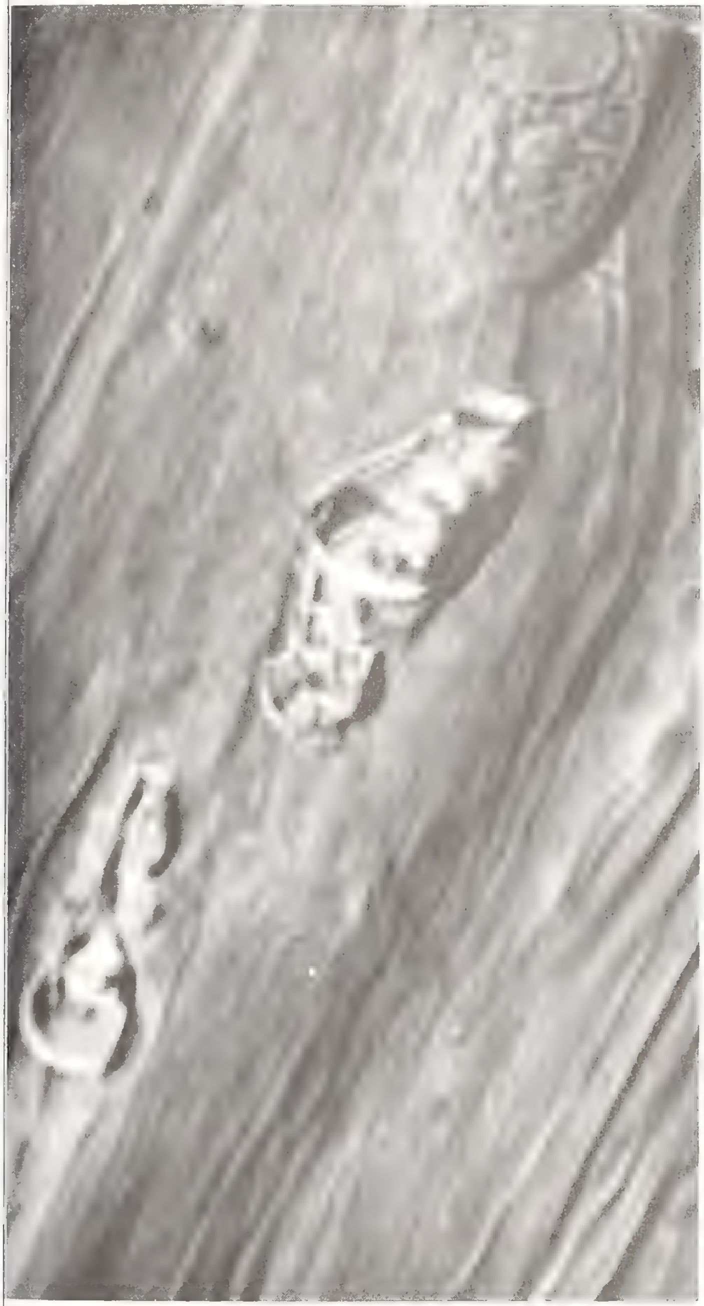
translucent head of a Xenopus tadpole its the easy visualization of optic e damage, which is pictured here ified eight times. (NIH Photo#1565)

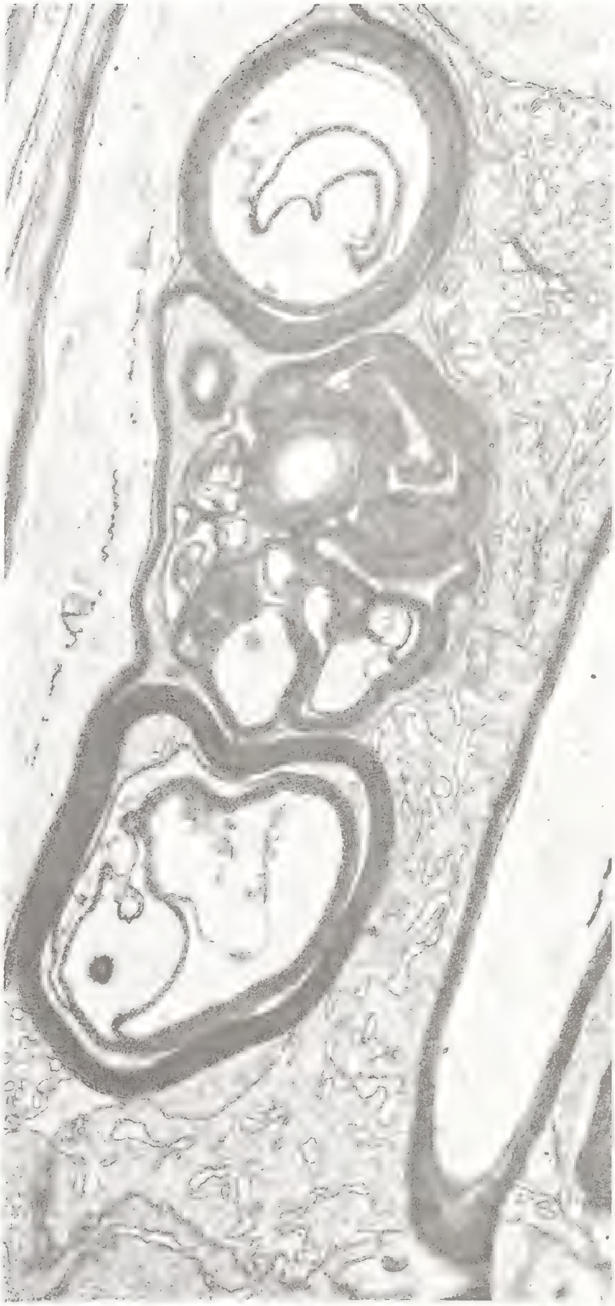


A Xenopus tadpole and the syringe used to inject the cerebrospinal fluid from multiple sclerosis patients. (NIH Photo# 1566)

TADPOLE (CONT'D)



As magnified 3000 times by the differential interference microscope, the tadpole's right optic nerve, in whole mount, displays demyelination lesions in the raised portions. (NIH Photo# 1567)



As magnified 15,000 times by the electron microscope, the rounded bodies represent lesions restricted to the myelin sheath. On either side the long, loaf-shaped nerve axons are undamaged. (NIH Photo#1568)

#

Research Advances

CELLS OF URTICARIA PATIENTS FOUND DEFECTIVE IN RELEASING ONE CHEMICAL

Grantees of the National Institute of Allergy and Infectious Diseases have found that cells of patients with chronic urticaria, or hives, are defective in releasing a chemical known to attract cells called eosinophils to the site of an immune reaction. Since these cells are thought to have a modulating effect on allergic reactions, a defect in release of eosinophil chemotactic factor (ECF) may partly explain the persistence of symptoms in patients with chronic urticaria.

Urticaria--also known as hives or nettle rash--is characterized by intensely itching wheals surrounded by reddened borders. The wheals may be localized or may occur over much of the body. In many cases, the cause is unknown but the condition is generally believed to result from an allergy to an inhalant or food. Drugs, such as penicillin or aspirin, may also induce urticaria. Other causes are mechanical pressure and exposure to light, heat, and cold.

In studying mechanisms involved in the induction of urticaria and other allergies, scientists have been focusing on the release of chemical mediators from certain white cells as the result of reaction between the allergen (antigen) and antibody. It is believed that a better understanding of these factors may lead to the development of improved ways to prevent or treat allergies.

In the present study, doctors at Johns Hopkins University School of Medicine studied white cells taken from 15 patients with chronic urticaria of unknown cause which had persisted for more than six weeks. Cells from 16 normal volunteers and from 12 ragweed allergic individuals were also

(more)

studied.

The scientists confirmed earlier findings that considerably smaller amounts of the chemical mediator, histamine, were released by white cells of urticaria patients than by cells of normal individuals or those with ragweed allergy. In addition, the Baltimore scientists found that ECF release was also defective in chronic urticaria patients. Since the number of white cells in the blood of urticaria patients seemed to be normal, the investigators suggest that the secretory mechanism of the cells, at least as it relates to the release of mediators, is generally suppressed in urticaria.

Eosinophils are prominent in many allergic reactions and their numbers are often increased in skin reactions associated with parasitic diseases or drugs. They are not only thought to have a modulating effect on allergic reactions but to contain inhibitors of histamine release and of another mediator--the slow-reacting substance of anaphylaxis.

Report of this work by Drs. Beate M. Czarnetzki, Frank Kern, and Lawrence M. Lichtenstein was published in the August 1976 issue of the *Journal of Investigative Dermatology.*

#

October 25, 1976

NEWS & FEATURES From NIH

Research Advances

CAUSE SOUGHT FOR HYPOGONADISM IN CERTAIN MALNOURISHED MALES

A Maryland grantee of the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD), in studies of gonadal function in men with severe protein-calorie malnutrition, has shown that the hypogonadism associated with this condition results primarily from markedly diminished secretion of testosterone by the Leydig cells of the testes.

Hypogonadism has been reported consistently in men with severe protein-calorie malnutrition, but opportunities to study gonadal function in such undernourished subjects have been rare. The present investigators were recently enabled to investigate the pituitary-gonadal axis in 28 affected Indians in a Calcutta hospital, both before and after two-to-five months of refeeding the patients with a high-calorie, high-protein diet.

The evidence obtained indicates that hypogonadism in malnutrition results primarily from diminished function of the testosterone-secreting Leydig cells of the testes. This is associated in many patients with hypersecretion of luteinizing hormone (LH), the pituitary hormone which controls testosterone secretion in the male.

Virtually all patients had the marasmic kwashiorkor type of protein-calorie malnutrition, their average weight being reduced to 74 percent of that attained after refeeding. All had clinical evidence of hypogonadism, including diminished body hair, beard growth, and libido. Plasma samples were analyzed before and after the refeeding period, and, in ten patients, before and after administration of human chorionic gonadotropin (HCG) for three days to stimulate testosterone secretion.

During refeeding, all patients showed substantial clinical recovery,

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including gains in weight and strength, increased body hair growth, and reappearance of libido. Plasma testosterone levels, which were low during malnutrition, increased to normal levels, but plasma LH, which was elevated in malnutrition and fell during refeedings, was persistently elevated after refeeding. HCG produced subnormal increments in plasma testosterone both in malnutrition and after refeeding.

Despite apparent clinical recovery of gonadal function in these patients after refeeding, pituitary-gonadal axis studies were consistent with a partially persistent, diminished Leydig cell function, associated in many patients with compensatory elevation of plasma LH levels. The fact that some testosterone values were in the normal range suggests that malnutrition *per se* may have produced symptoms and/or physical findings of hypogonadism in some patients.

NIAMDD grantee Dr. Claude J. Migeon of Johns Hopkins University, and associates, reported their study in the *Journal of Clinical Endocrinology and Metabolism.*

#

Research Advances

SPECIAL FAST TRIED FOR ADULT-ONSET DIABETICS

A Massachusetts grantee of the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD) has shown in preliminary clinical trials that maintaining obese adult-onset diabetics solely on a protein-sparing modified fast allows effective control of carbohydrate metabolism and hunger. The regimen permits withdrawal of exogenous insulin and is associated with marked weight loss.

It is well-known that weight loss in the obese has a beneficial effect on pancreatic endocrine function. Unfortunately, diet therapy seldom achieves weight reduction in the obese and such therapy becomes complicated in the insulin-dependent diabetic. The investigators recently reported marked weight reduction in obese normal subjects through use of a protein-sparing modiefied fast (PSMF), and now report similar success in obese, adult-onset *diabetics* who ordinarily were receiving 30-100 units of insulin daily.

PSMF therapy was associated with significant weight reduction, reduced serum glucose and insluin levels, and increased free fatty acid and ketone body concentrations. Therapeutic insulin could be withdrawn after 0 to 19 days and a positive nitrogen balance was maintained. For diabetics with some endogenous insulin reserve, the PSMF offers significant advantages for weight reduction, including preservation of lean body mass and withdrawal of exogenous insulin.

Seven obese adult-obese diabetics who were receiving 30 to 100 units of insulin/day were treated and followed for one year. The PSMF is a total fast modified by intake of 1.2 to 1.4 gm protein/kg of ideal body weight,

(more)

fluids *ad libitum*, and vitamin and mineral supplementation.

A typical patient was a 60-year-old female weighing 226 pounds, who had had diabetes for 11 years. She received 55 units of insulin/day and her serum glucose was 178 mg/100 ml. This inpatient initially began the PSMF at 99 gm protein/day and her insulin was discontinued simultaneously. Blood sugar levels remained normal and nitrogen balance was positive. She was discharged after 15 days and readmitted periodically for reevaluation. Glucose, insulin, and triglyceride levels dropped while free fatty acids and serum and urinary ketones increased. Weight loss after ten months of PSMF therapy was 83 pounds.

The PSMF was well tolerated by all patients, excellent control of carbohydrate metabloism was achieved, and five of seven patients lost more than 40 pounds each. Side effects, which were transitory, included mild postural hypotension, lowering of blood urea nitrogen levels, and increased serum uric acid levels. NIAMDD grantee Dr. Bruce R. Bistrian of the New England Deaconess Hospital, Boston, and associates reported their findings in *Diabetes*.

#

Photo Feature

DR. GAJDUSEK IS SHOWN
IN 1956 AND IN 1976

Dr. D. Carleton Gajdusek of the NIH in New Guinea doing field research on slow virus disease in 1956. (NIH Photo #1569)

Dr. Gajdusek is shown at the NIH Press Conference on October 14, 1976, after the announcement of his winning a Nobel Prize. (NIH Photo #1570)

#

News Feature

TOURETTE'S SYNDROME IS THE CURSING SICKNESS

Tourette's syndrome is one of the most bizarre diseases known to medicine. It is probably not a psychological problem, as doctors once believed, but a disorder due to a chemical imbalance in the central nervous system. Victims do not necessarily come from unhappy or repressive homes, and the disease can be found in every race and culture and at every intelligence level.

Tourette's syndrome is named after the French physician Georges Gilles de la Tourette, who described it in detail in 1885. The victim of the disease was a noblewoman who was so humiliated by the symptoms of her malady that she cut herself off from all social contact for 70 years of her life. Since 1885, 500 cases of the disease have been recorded in medical literature. At least 300 people are known to suffer from the disease today, but the number of unreported cases may number in the thousands.

The onset of Tourette's disease typically occurs in childhood, between the ages of two and 15. It often begins with uncontrollable twitching of the face that gradually becomes worse and may affect other parts of the body such as the feet and hands. The twitching is followed by involuntary noises such as grunting or barking, or the patient may repeatedly echo words that he has heard. As the disease progresses, the patient may have outbursts which include vulgar and obscene language.

The young patient may appear preoccupied with sexual impulses, frequently handling his genitals, exposing himself at home, or attempting intimate touching of his mother. Sometimes the child has a similar preoccupation with aggressive impulses. He may bang his head against a wall or slap

(more)

himself, or he may be unusually rough in his play. Fortunately, these symptoms may disappear and seldom lead to any serious anti-social behavior.

The syndrome affects boys more frequently than girls and the symptoms are often less dramatic in female patients. While not clearly a genetic disease, it may be influenced by genetic factors. Scientists have found at least 40 families in which two or more members have the syndrome.

The symptoms of Tourette's disease have led many people to believe that it is a mental disorder. In earlier days, victims of this disease were believed to be possessed by the devil. In more modern times, it has frequently been misdiagnosed as schizophrenia and its victims have been relegated to mental institutions. According to Dr. Roswell Eldridge of the National Institute of Neurological and Communicative Disorders and Stroke, Tourette's disease is in no way related to intelligence, nor is it a prelude to a psychotic state. In spite of this, many Tourette patients find it difficult to live a normal life, expecially if their condition has not been recognized for what it is. They may be feared and avoided by society, unable to hold down jobs or find marriage partners, and are often misunderstood and discriminated against, even by their families and closest friends. Those who do marry are unable to have any kind of a social life and often cause hardships for their spouses and children.

There are a number of other nervous disorders which cause symptoms similar to those of Tourette's syndrome. Children sometimes develop facial or bodily twitches, called tics, as a nervous habit. Tics are generally outgrown. Tourette's syndrome can be recognized by three specific symptoms:

(more)

multiple facial and bodily tics, involuntary expressions or sounds, and onset in childhood. A fourth symptom present in many cases is the unusual preoccupation with sexual play. If all four of these symptoms are present, there is strong indication that the patient is suffering from Tourette's syndrome.

Until recently, there was no cure for Tourette's syndrome. Even today, it is not unusual for Tourette patients to go to may doctors without getting a correct diagnosis. Many sufferers spend thousands of dollars on psychotherapy, which probably does nothing to cure the disease although it may help the patient to adjust to his fate.

It is only within the past ten years that a drug has been found that seems to be effective in the treatment of Tourette's syndrome. The drug, haloperidol, blocks the action of certain chemicals that transmit messages in the brain. It has been used most extensively by Dr. Arthur K. Shapiro, a psychiatrist at New York Hospital's Payne Whitney Clinic and a professor of psychiatry at Cornell University. Dr. Shapiro, who has seen over 100 such patients at New York Hospital, reports that about 25 percent of the patients treated with haloperidol make a complete recovery and another 50 percent attain substantial relief. The remainder are not helped at all by the drug. Although the side effects caused by the drug may be troublesome, haloperidol has offered a new life to many sufferers of Tourette's syndrome. Other drugs are now being tested in the hope of decreasing the side effects and increasing the number of patients that can be helped.

In order to inform physicians and the public about this mysterious disease, the Tourette Syndrome Association was formed in 1972. From its headquarters in Queens, New York, the Association dispenses information to

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anyone who wants to learn more about the disease and gives assistance and counseling to those who are affected by it.

Anyone who has the four symptoms of Tourette's syndrome should first be seen by the family doctor. The doctor may refer the patient to a neurologist or other specialist for treatment. The patient or his family may also wish to contact the Tourette Syndrome Association at 42-40 Bell Boulevard, Bayside, Queens, New York.

The precise causes of Tourette's syndrome are not yet known. However, because of the way the disease reacts to haloperidol, scientists suspect that the disease is related to a chemical deficiency in the brain. Since a single drug is useful in treating the disease, it may be that a single chemical abnormality is present.

Research into the causes and cures of Gilles de la Tourette's syndrome is of great interest to scientists in the field of neurology and psychology. If more can be learned about the organic causes, it may lead to a greater understanding of the chemistry of the brain. This knowledge may then be applied to certain psychological disorders that are thought to be related to organic deficiencies. Thus, it is hoped that further research may not only prove helpful to sufferers of Tourette's syndrome, but may also reap benefits for victims of other psychological and neurological disorders.

#

News Feature

NEW INSTRUMENT HELPS SPEECH SCIENTISTS COMPARE FINDINGS

An instrument called Tonar II can measure and give a numerical score to the voice quality recognized by the human ear as nasality. Speech scientists in different laboratories should now be able to make better comparisons of their research observations.

With support from the National Institute of Dental Research, Samual G. Fletcher, Ph.D., of the University of Alabama, Birmingham, has compared the ability of humans and the machine to rank serially the speech of cleft palate children as ranging from normal with little nasality to pathological and extremely nasal. Twenty college students listened to standard recorded speech of 23 children who had repaired cleft palates, and ranked each child in a continuum from normal to most nasal. None of the listeners possessed expertise concerning abnormal speech, yet after many hours of listening, they reached a 75 percent level of agreement in their evaluations.

Sound-separated recordings of the same children saying the same words were played through Tonar II. Dr. Fletcher found that a 10-second, time-constant filter produced an averaged curve which gave the best score of *nasalance*. Nasalance is a name for the relative proportion of sound from the nose and the mouth within a specified frequency band during speech.

The listeners and Tonar II reached sufficient agreement to indicate that the machine can provide a valid assessment of nasality, and is capable of quickly and quantitatively ranking numerous speakers. It could eliminate the need for a costly and time-consuming process of evaluation. The machine should also make findings in one speech laboratory numerically comparable with results in another.

This research was reported in the *Cleft Palate Journal*.

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EWS & FEATURES From NIH

October 25, 1976

News Feature

AREFUL TESTS PLANNED FOR NEW RUG TO DISSOLVE GALLSTONES

Large-scale testing of a new drug to dissolve gallstones without surgery as been initiated with changes in the eligibility requirements for patients.

Dr. Leslie J. Schoenfield of Cedars-Sinai Medical Center, director of the National Cooperative Gallstone Study, said the rule changes qualify ore women and older persons for treatment, greatly expanding the scope of the study.

Approval for the NCGS to proceed on September 1, 1976 has been given by the National Institutes of Health (NIH) and the Food and Drug Administration (FDA) based on the satisfactory completion by the NCGS of short and long-term animal testing and in the completed accession of 100 patients to an initial study which includes liver biopsies for assessment of hepatic morphology.

The major criteria for admission of patients to the study are:

1. The presence of gallstones in a gallbladder seen on a gallbladder X-ray.
2. The patient is either a woman in menopause, after hysterectomy, or tubal ligation, or over age 40 using an IUD for contraception, or a man between 21 and 79 years of age.

   The major exclusion criteria include current excessive obesity, (200 percent of ideal body weight), liver disease, inflammatory bowel disease, severe heart disease, or malignancy.

The two most important changes in patient eligibility requirements are:

1. The inclusion of women 40 years of age and older using IUD's for contraception (formerly women capable of bearing children were excluded).

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2. The extension of the upper age limit for patients from 70 to 79 years. These liberalizations in criteria will allow more patients with gallstones for whom medical dissolution therapy is relevant to be included in the clinical trial.

During the first phase of the NCGS, a protocol and procedures manual were developed, Treatment Centers and a supplier for chenodeoxycholic acid were selected, and animal toxicology studies were instituted. The second phase began in January 1976 with Treatment Centers entering patients into the study which includes liver biopsies.

The Coordinating Center for the NCGS under the direction of Dr. Leslie J. Schoenfield is located at the Cedars-Sinai Medical Center in Los Angeles. The 10 Treatment Centers of the NCGS are: University of California, San Francisco (Dr. David Earnest); Yale University Medical School, New Haven, Connecticut (Dr. Henry J. Binder); University of Minnesota, Minneapolis (Dr. Russell F. Hanson); Scott and White Memorial Hospital, Temple, Texas (Dr. N.C. Hightower); The New York Hospital, Cornell Medical Center, New York (Dr. Norman B. Javitt); Emory University, Atlanta, Georgia (Dr. Theodore Hersh); University of Pennsylvania Medical School, Philadelphia (Dr. Roger D. Soloway); Mayo Clinic Medical School, Rochester, Minnesota (Dr. Johnson L. Thistle); Duke University Medical Center, Durham, North Carolina (Dr. Malcolm P. Tyor); and Cedars-Sinai Medical Center, Los Angeles (Dr. Martin J. Coyne).

Cholesterol gallstone disease (most gallstones are composed primarily of cholesterol) is extremely common in the United States. Approximately 20 million people have cholesterol gallstones which furthermore, are newly

(more)

discovered in one million persons yearly. About 500,000 cholecystectomies (operations to remove the gallbladder and gallstones) are performed annually. Cholecystectomy is an effective and relatively safe procedure but the alternative of medical dissolution will be appropriate for many patients with gallstones.

Cholesterol gallstones form because bile contains more cholesterol than can be solubilized by the bile acids and lecithin in the bile. Administration chenodeoxycholic acid, a bile acid normally found in human bile, increases the capacity of bile to dissolve cholesterol.

Although a number of small studies have indicated that administration of capsules of chenodeoxycholic acid is effective in dissolving cholesterol gallstones, a large controlled study is necessary to definitively establish the efficacy, safety, and optimal dosage level of chenodeoxycholic acid.

In preliminary investigations throughout the world, no evidence of significant toxicity has been observed in human subjects. Injury to the liver, however, has occurred in monkeys treated with higher doses of chenodeoxycholic acid than is being used in the cooperative clinical trial. Thus, despite the apparent lack of toxicity in humans, the findings in animals warrant careful monitoring of the patients participating in the NCGS.

The major goals of the study are:

* To establish the efficacy and safety of two dosage levels of chenodeoxycholic acid for gallstone dissolution.
* To establish the natural history of gallstone disease.
* By ancillary studies to gain further understanding of bile acid metabolism, gallstone formation, and the mechanism of action

(more)

of chenodeoxycholic acid.

Nine hundred additional patients (90 at each center) will be randomly allocated into three treatment groups. One group will receive a low dose of chenodeoxycholic acid (375 mg. per day) which has been shown to induce favorable changes in bile but which has not yet been tested in clinical trials for gallstone dissolution. A second group will receive a higher dose of chenodeoxycholic acid (750 mg. per day), a dose which from previous studies is known to be effective in gallstone dissolution. Finally, a control group will receive placebo (inactive material) and provide information on the natural history of untreated gallstone disease for comparison with the treated patients.

All patients who are to be considered for inclusion into the study are to be referred to the Treatment Center by their personal physician who will continue the general care of his patient while receiving periodic reports from the center of his patient's progress in the study. The patients will be followed for two years with periodic examinations, blood tests, necessary X-rays, and duodenal drainage for determination of bile composition.

In order to assure objectivity, the study will be conducted in a double-blind fashion so that neither the patient nor his Treatment Center physician will know which of the treatments the patient is receiving until the end of the study. The code of treatment, however, will be available to another representative physician at each center.

All expenses for examinations, tests, and treatment related to the experimental program will be covered by the Treatment Center. The expense of treatment for incidental illnesses unrelated to chenodeoxycholic acid therapy or for recognized complications of gallstone disease including cholecystectomy, however, will not be covered by the program.

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NEWS & FEATURES From NIH

October 25, 1976

News Feature

CERTAIN THYROID X-IRRADIATION IS POSSIBLE CAUSE OF TUMORS

Exposure of the thyroid gland to external beam X-irradiation or to radium plaques during the treatment of various nonmalignant conditions of the head, neck or upper thorax in infancy and childhood is now recognized as a possible cause of the development of both benign and malignant tumors of the thyroid many years later, according to the National Cancer Institute.

For several decades beginning in the 1920's, radiation therapy was considered good medical practice and very effective treatment for patients with such conditions as enlargement of the thymus gland, hypertrophy of tonsils and adenoids, deafness due to hypertrophied lymphoid tissue around the Eustachian tubes, cervical adenitis, hemangiomas of the head and neck, tinea capitis and acne.

A linkage of thyroid tumors with prior irradiation was not recognized until these tumors began to be diagnosed with increasing frequency in individuals more than five years after the initial treatment.

It is now recognized that the effect continues into adult life, and that anyone with a history of such prior irradiation is at significantly increased risk of developing thyroid tumors. Intervals of more than 35 years between irradiation and diagnosis have now been recorded.

Fortunately, the tumors produced are generally slow-growing and benign. Even when malignant, they usually remain confined to the neck for long periods and can be successfully removed surgically.

The greatest problem is to identify those individuals who actually received irradiation to the head or neck in childhood and should now be subjected

(more)

to careful examination and continuing followup. Many individuals do not know whether or not they received such irradiation and the records of treatment given so many years ago may no longer be available. Any hospital which has suitable records for tracing such patients is strongly encouraged to initiate a recall program, but in general, the best means of alerting the irradiated population will be a carefully planned public education program about the problem.

Any individual who thinks he may have had such irradiation - as well as anyone who feels a lump in his thyroid gland - should be encouraged to visit his physician or usual source of medical care for an examination.

The most important part of the examination is the inspection and palpation of the thyroid gland. Tests of blood or other body fluids are not useful in the differentiation of benign from malignant nodules.

There is some disagreement on the value of radioisotope scans, but many physicians consider them helpful, since "cold" nodules (i.e., those which do not accumulate radionuclide) are more likely to be carcinomas. A scan may also reveal a small lesion which can not be detected by palpation.

A trial of thyroid hormone administration may be used to shrink the thyroid gland and thereby make palpation of a doubtful nodule more definite. Thyroid hormone may also be given in the treatment of diffuse enlargement of the thyroid. Some authorities consider it worthwhile to offer thyroid hormone to asymptomatic patients with a history of head or neck irradiation in the hope of preventing the development of thyroid tumors.

In general, surgical exploration should be considered for all palpable thyroid nodules, particularly those which are firm and clearly demarcated

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and those which are "cold" on scan.

All individuals who are at risk because of prior radiation to the head or neck, and those who have already been treated surgically for a thyroid malignancy should be followed with regular reexamination every one to two years.

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NEWS & FEATURES From NIH

October 25, 1976

News Feature

PHS ANNOUNCES NATIONAL IMMUNIZATION CONFERENCE

The Public Health Service will hold a national public meeting in mid-November to review Federal policy questions regarding vaccines and immunization, Assistant Secretary for Health Theodore Cooper announced today.

The National Immunization Converence, which will be held in Bethesda, Md., November 12, 13, and 14 will be open to the public, with active public participation invited.

Among the issues to be examined during the three-day meeting will be allocation of resources for immunization; the role and responsibilities of Federal, State, and local Government; adequacy of current legislation; supply, safety, and effectiveness of vaccines; the nature of recommendations to the public; marketplace difficulties from the manufacturers' point of view, informed consent and compensation; liability issues; the implications of advances in vaccine technology for closing of immunization gaps in the future and methods of public education.

These questions will be examined in the light of experience gained in the present National Influenza Immunization ("swine flu") Program as well as of recent questions raised about the adequacy of the vaccine supply for other diseases.

The conference is aimed at the development of future national immunization policies which will assure an adequate supply of vaccine against present and emerging diseases.

Private citizens wishing to address the conference should submit a

(more)

CONFERENCE (CONT'D)

text of their comments by November 5. Time for public comment will be limited, so requests to give oral presentations will be accepted on a first come basis. While written comments may be of any length, oral presentations will be limited to five minutes in order to accommodate as many as possible.

Send submissions to:

Mr. John M. Blamphin
Director of Public Affairs
Room 731G-2
South Portal Bldg.
200 Independence Ave. S.W.
Washington, D.C. 20201

The conference will be held in the main auditorium of the Clinical Center, National Institutes of Health, Bethesda, Maryland.

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NEWS & FEATURES From NIH

October 25, 1976

News Feature

NIH ISSUES SOME DOCUMENTS RELATED TO DNA GUIDELINES

The National Institutes of Health has issued Recombinant DNA Research, Vol. 1--Documents Relating to "NIH Guidelines for Research Involving Recombinant DNA Molecules," February 1975- June 1976. The 600-page publication is available in some 660 public libraries throughout the country and is sold by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402, at $6.90 (Stock No. 017-040-00398-6).

Prepared by the NIH Office of Program Planning and Evaluation in August, this is a public record of correspondence, proceedings of conferences, guidelines proposed and released, public announcements, etc., documenting the role of NIH in the development and promulgation of the guidelines of June 23, 1976.

#

NOTE TO SCIENCE WRITERS:

Current research on hypertension, risk factors in hardening of the arteries, and new methods of diagnosing heart disease and treating heart attacks will be presented at a:

SCIENCE WRITERS SEMINAR ON CARDIOVASCULAR DISEASES

Wednesday -- November 10, 1976
2:00 -- 4:30 p.m.

National Institutes of Health
Building 31-A, First Floor, Conference Room 4
Bethesda, Maryland

****

PROGRAM

I. Vasoactive Systems and Hypertension.
Harry R. Keiser, M.D., Clinical Director, Division of Intramural Research, National Heart, Lung, and Blood Institute

II. High Density Lipoproteins (HDL) as a Risk Factor in Atherosclerosis.
H. Bryan Brewer, Jr., M.D., Chief, Molecular Disease Branch, Division of Intramural Research, National Heart, Lung, and Blood Institute

III. Radionuclide Cine-angiography: A Sensitive New Technique in Diagnosing and Evaluating Therapy for Persons with Heart Disease.
Jeffrey S. Borer, M.D., Senior Investigator, Cardiology Branch, Division of Intramural Research, National Heart, Lung, and Blood Institute.

IV. Treatment of Heart Attack
Stephen E. Epstein, M.D., Chief, Cardiology Branch, Division of Intramural Research, National Heart, Lung, and Blood Institute

****

PRESENTED BY THE INTRAMURAL SCIENTISTS OF THE NIH
and
The Division of Public Information, NIH
Irving Goldberg, Director

Parking spaces will be available, and coffee will be served before the program. For general information, call Angela Martin, (301) 496-2535. For program details, call Jane Collins, Seminar Coordinator, (301) 496-9151.

#

Editors of publications may request a glossy print of the numbered photographs that appear in this issue.

Ms. Joyce Flaherty
National Institutes of Health
Building 31, Room 2B-10
Bethesda, MD 20014

Dear Ms. Flaherty:

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See page 18

RESEARCH ADVANCES:

Cholesterol-Lowering Drug Used for Kepone Detoxification............1
Cine-Angiography Views Heart During Exercise.....5
Chimps with Chronic Hepatitis B Treated with Interferon Inducer........7

NEWS AND PHOTO FEATURES:

Waterbeds Help Reduce Breathing Cessation in Premature Infants...9
Joint US-USSR Study Begun of Penicillin Treatment for Arthritis...13
Acupuncture's Pain-Killing Effect Blocked by Morphine Antagonist...15
Tiny Tim, a Lemur, Is Born in Oregon.......................18
Severity of Diarrhea in Cholera Linked to Nutritional Status...20
Childhood Malnutrition Affects Learning, Motivation, and Attention Span..................................22
Notice to Medical and Dental Students about NIH Appointments...24

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Research Advances

CHOLESTEROL-LOWERING DRUG USED FOR KEPONE DETOXIFICATION

Investigators at the Medical College of Virginia, Richmond, are in the midst of a four-month study to determine if the drug cholestyramine can help eliminate the pesticide Kepone from the body. The clinical trial follows a preliminary study which suggested that the drug, often used as a cholesterol lowering agent, also can increase Kepone elimination.

Information on the initial study and current clinical trial was presented November 4, 1976, at a meeting of the American Association for the Study of Liver Diseases in Chicago by Dr. Philip S. Guzelian, a liver specialist at the Medical College of Virginia, the health sciences division of Virginia Commonwealth University.

Both the preliminary study and the current clinical trial have been carried out in the Clinical Research Center of the Medical College of Virginia. The clinical research center is one of 82 such units funded by the NIH Division of Research Resources. These miniature research hospitals within larger hospitals provide highly specialized patient-centered research facilities to the entire staff of the institutions where they are located.

According to Dr. Guzelian, seven patients were given cholestyramine for one week and produced almost seven times more fecal elimination of Kepone as compared to patients not given the drug. Dr. Guzelian and his colleagues are now studying to find out why cholestyramine induced the increased elimination.

Dr. Guzelian explains that possible flaws in the methods of measuring Kepone quantities may make it appear that more Kepone is being eliminated although actual body levels of the pesticide do not significantly change. He also says that none of the seven patients in the earlier study showed

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any improvement in their symptoms while taking cholestyramine.

"It might just be a chemical phenomenon," the researcher says. "We just don't know. We only gave the drug for one week to see if it would have any effect. We were encouraged by the results so we began this clinical trial."

The current study involves 32 patients who have been exposed to large quantities of Kepone for four weeks up to one year while working at a now closed Hopewell, Virginia, plant that produced the pesticide. The patients all exhibit common manifestations of Kepone poisoning--tremors, mild liver problems, and decreased sperm production. Most are being treated as outpatients, according to Dr. Guzelian.

During a year of research conducted under an NIH contract which calls for finding a method to rid the body of Kepone, Dr. Guzelian and his colleagues discovered that about 10 percent of the Kepone entering the intestine in bile from the liver was eliminated in the patients' stools. "The big question is where did the other 90 percent of the Kepone go," he says. "Something in the intestine may have modified the Kepone into another component or the Kepone may have been reabsorbed in the blood stream where it would again enter the liver and return to the intestine.

"We believe cholestyramine stimulated the elimination of Kepone by binding the pesticide in the intestine to prevent its absorption. We have not yet ruled out the possibility that the drug prevented the metabolism of Kepone into another component in the intestine or that it altered chemical measurement of Kepone."

If cholestyramine does prevent the reabsorption of Kepone from the intestine into the blood stream, the drug may accelerate depletion of Kepone

(more)

from tissue stores in the body and thus may provide a means of detoxification for Kepone poisoning and perhaps poisoning from similar pesticides, Dr. Guzelian explains.

During the current clinical trial, half of the patients are receiving cholestyramine while the other half receive a placebo. Dr. Guzelian explains that the investigators are highly interested in finding out if increased Kepone elimination continues in patients receiving the drug, what is causing the increased elimination, and if the patients demonstrate signs of recovering from the illness.

He points out that such research is ideally suited for the clinical research center facility where the drug under study can be properly administered, body samples carefully analyzed in special laboratories, and the patients' health continuously monitored.

Doctors had feared that Kepone poisoning was irreversible and, in addition, that Kepone could cause cancer when stored in human tissue since it already has produced liver cancer in rodents during laboratory studies.

Even though the preliminary study was encouraging, Dr. Guzelian continues to vigorously caution against unwarranted optimism. "The findings thus far are very preliminary. The four-month study, which will end in January, should give us more information as to whether we're on to something here."

(more)

KEPONE (CONT'D)

Dr. Philip S. Guzelian conducts precise measurements of body samples in the special Kepone Research Laboratory at the Medical College of Virginia, Richmond. Dr. Guzelian is in the midst of a four-month study to see if the drug cholestyramine can help eliminate the pesticide Kepone from the body. The clinical trial is taking place in the medical college's clinical research center, one of 82 such units funded by the NIH Division of Research Resources. (NIH Photo# 1571)

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Research Advances

CINE-ANGIOGRAPHY VIEWS HEART DURING EXERCISE

A new technique to identify persons with coronary artery disease and to assess myocardial ischemia physiologically has been developed at NIH by Dr. Jeffrey S. Borer of the Cardiology Branch, National Heart, Lung, and Blood Institute, and Michael V. Green and Dr. Stephen L. Bacharach of the Nuclear Medicine Department of NIH's Clinical Center, and Dr. James J. Bailey and Harold G. Ostrow of NIH's Division of Computer Research and Technology.

The technique permits viewing the heart by computer-based movies during and immediately after exercise. The approach offers relatively little discomfort to the patient. Serum albumin tagged with a small amount (10 millicuries) of a radioactive label (^{99m}technetium) is injected into a peripheral vein. A few minutes later an instrument to measure radioactivity is placed on the patient's chest. Emissions are localized by a computer while the patient is at rest or exercising, and displayed simultaneously as a motion picture and as a time-activity curve indicating precise changes in left ventricular volume with time.

Using this new method during exercise, the investigators have been able to detect abnormalities diagnostic of coronary artery disease even in asymptomatic patients who have normal cardiac function at rest. Moreover, in persons with known coronary artery disease, they have been able to assess the degree of functional impairment caused by specific coronary artery lesions, and to evaluate the effects of therapy.

In studies performed at the National Institutes of Health in over 150 patients, the radionuclide cine-angiography technique has proved to be both sensitive and accurate in assessing abnormalities in myocardial function, at rest and during exercise.

(more)

Dr. Borer noted that the procedure offers less risk than cardiac catheterization, and unlike the latter method, can be performed during exercise.

Moreover, he cited its advantages over the exercise electrocardiogram, which lacks predictive value in asymptomatic persons and is only moderately sensitive in symptomatic patients.

The technique was announced at the American Heart Association meeting in Miami on November 15, 1976.

#

Research Advances

CHIMPS WITH CHRONIC HEPATITIS B TREATED WITH INTERFERON INDUCER

National Institute of Allergy and Infectious Diseases scientists and their colleagues have reported temporarily successful use of a chemical in treating chimpanzees with chronic hepatitis B virus infection.

The chemical used, PICLC (polyriboinosinic-polyribocytidylic acid-poly-l-lysine carboxymethyl cellulose), induces interferon, and antiviral substance produced by the body. Interferon can also be produced in the laboratory from human white blood cells, but it is difficult to obtain and is very expensive. Scientists have been seeking an effective and relatively inexpensive inducer to increase production of endogenous interferon to fight viral infection. PICLC is one of the most promising inducers at the present time in that it is only moderately toxic and is not readily broken down by the body.

As reported in the October 9, 1976, issue of *Lancet*, Dr. Robert H. Purcell and his associates used PICLC, a stabilized derivative of an earlier inducer, poly I:poly C, in a study with four chimpanzees. PICLC significantly reduced the number of Dane particle markers in the blood that indicated hepatitis B infection. Dane particles are thought to represent the complete hepatitis B virus.

The scientists' success in treating the chimpanzees was only temporary in that cessation of therapy resulted in markers of infection returning to pretreatment levels. Dr. Purcell and his co-workers believe, however, that their failure to cure the animals may have been due to their inability to maintain constant serum levels of interferon in the experimental animals.

(more)

HEPATITIS B (CONT'D)

The results closely parallel findings recently reported by NIH grantees and by European scientists who administered exogenous interferon to chronically infected humans. It has not yet been determined in any of the studies whether suppression of Dane particle production also limits the infectivity of the hepatitis carrier.

The studies further indicated that the hepatitis B virus itself is a relatively poor stimulator of interferon production, perhaps accounting for the chronicity of the disease. However, even small amounts of interferon suppress virus synthesis.

These results show that PICLC (or exogenous interferon) may be useful in treating chronic hepatitis B virus infections in humans. It has been estimated that at any one time between 150 and 200 million of the world's population are infected with hepatitis B virus. Most of these are chronically infected, and thus, are potential carriers of disease, posing a major threat to world health.

This study was reported by Drs. Robert H. Purcell, NIAID, John L. Gerin, Molecular Anatomy Program of Oak Ridge National Laboratory, William T. London, NINCDS, JoAnn Wagner, NIAID, Vincent J. McAuliffe, NIAID, Hans Popper, Mt. Sinai School of Medicine, New York, Amos E. Palmer, NINCDS, Eduard Lvovsky, NIAID, Paul M. Kaplan, Molecular Anatomy Program, Doris C. Wong, NIAID, and Hilton B. Levy, NIAID.

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Photo Feature

WATERBEDS HELP REDUCE BREATHING CESSATIONS IN PREMATURE INFANTS

Researchers at Stanford University Medical Center have found that placing premature infants on waterbeds significantly reduces temporary breathing cessations, a problem common in premature babies.

The waterbed research has been conducted in the Stanford General Clinical Research Center since 1972 by Dr. Anneliese F. Korner, adjunct professor in the Department of Psychiatry and Behavioral Sciences. The General Clinical Research Center is supported by the NIH Division of Research Resources.

The Stanford research demonstrates that premature infants placed in incubators equipped with waterbeds had fewer stop-breathing episodes, called apneic spells, than premature infants placed in standard incubators. The waterbed studies are the outgrowth of a decade of research by Dr. Korner and her collaborators which have shown that movement stimulation is much more potent in bringing about behavioral and developmental changes in newborns than is touch and body contact, long considered the most important form of stimulation for very young infants.

Premature infants are deprived of the movement stimulation normally brought about by their flotation in the uterus during a full-term pregnancy. The waterbeds are designed to make up for the movement stimulation missed by the prematurely born infant.

New research by Dr. Korner will attempt to determine if the movement provided by the waterbeds results in additional infant development benefits, such as better organized sleep patterns and a more intact motor and neurological development.

(more)

WATERBEDS (CONT'D)

Two styles of waterbeds have been developed by the Stanford researchers: one which allows the baby to experience the rocking effects produced by his or her own movements, and one which, in addition, mechanically provides gentle, irregular oscillations in the rhythm of maternal respirations.

The waterbeds are the same size as an incubator mattress, but they are somewhat deeper. The waterbed bag, filled with two gallons of warm water, is contained within the incubator in a plastic tray. The temperature of the water is maintained by the incubator's heating system. A highly elastic membrane covers the unit. Oscillation in those water beds which gently rock the infant is provided with the help of a compact, respirator-like unit.

The study shows that premature infants placed on the waterbeds have pulse and respiration rates, temperature, weight changes, and oxygen needs similar to infants in ordinary incubator environments. There have been no indications that the waterbeds have made any of the infants "seasick."

"Our original research showed that significantly fewer breathing cessations occurred in the babies on the waterbeds than among babies in a control group not on the waterbeds," Dr. Korner said. "We have since begun another study which reinforces our previous findings. In this study, being done in collaboration with Dr. Christian Guilleminault from the Stanford Sleep Disorder Clinic, the respiratory and sleep patterns are polygraphically recorded during periods while the same babies are on and off the oscillating waterbeds. The preliminary results of this study show that the infants have fewer breathing cessations on the waterbeds. We plan to look at these more recent studies in greater detail."

(more)

WATERBEDS (CONT'D)

Upcoming studies are being planned by Dr. Korner to determine the difference, if any, in benefits between the mechanically oscillating and non-oscillating waterbed.

"The non-oscillating waterbed has already been used extensively for a number of clinical purposes, mainly at the request of the nursing and medical staff," Dr. Korner said. "These beds have been found useful in maintaining the fragile skin of very small premature babies, and in the care of infants who are emaciated or recovering from abdominal surgery. Clinically, waterbed flotation seems beneficial in any condition in which pressure points to the skin or the skeletal structure are to be avoided."

(more)

WATERBEDS (CONT'D)

Dr. Anneliese Korner, adjunct professor of psychiatry and behavioral sciences at the Stanford University Medical Center, observes as an infant sleeps on an oscillating waterbed in the Stanford Intensive Care Nurseries. Dr. Korner's research on the use of waterbeds in reducing breathing cessations in premature infants was carried out at Stanford's General Clinical Research Center, a unit supported by NIH's Division of Research Resources. (NIH Photo # 1572)

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News Feature

JOINT US-USSR STUDY BEGUN OF PENICILLIN TREATMENT FOR ARTHRITIS

The United States and the Soviet Union have begun their first cooperative trial in the field of arthritis, according to Dr. Theodore Cooper, Assistant Secretary for Health.

He said that physicians in both countries will carry out identical studies on the use of the drug D-penicillamine in rheumatoid arthritis. The United States' program under the auspices of NIH, involves four New York City medical schools.

Penicillamine was first used for the treatment of rheumatoid arthritis in the United States over ten years ago by Dr. Israeli Jaffe of the New York Medical College. In the past five years, careful trials in Great Britain have supported its efficacy in treating serious forms of rheumatoid arthritis. In the present US-USSR cooperative study, lower doses of the drug will be compared with the more usual doses to see if they are effective. The participating scientists hope that some of the unwanted side-effects may be less common at lower doses. There has been extensive experience on the use of the drug in the United States and Great Britain but not yet in the Soviet Union.

The drug, a natural breakdown product of penicillin, has been successful in treating a rare illness of the liver and nervous system called Wilson's disease in which excessive copper accumulates in the body. D-penicillamine helps remove the copper. Its action in arthritis, however, does not seem related to this property.

The U.S. cooperative trial will be coordinated by Dr. Jaffe at the

(more)

New York Medical College and Drs. John Decker and Paul Plotz at the NIH's National Institute of Arthritis, Metabolism, and Digestive Diseases. The arthritis clinics at Columbia-Presbyterian Medical Center, The Hospital for Special Surgery of New York Hospital, and New York University Bellevue Medical Center will also participate in the trial.

In the Soviet Union, the trial will be coordinated by the Institute for Rheumatism of the Academy of Medical Sciences in Moscow under the direction of Professors M.G. Astapenko and E. Agababova. Supplies of the drug will be shipped very soon from the National Institutes of Health to the Institute for Rheumatism. At the end of the trial, data from both countries will be compared. By having the trial carried out identically among two quite different populations, the investigators hope to discover whether patients in both countries respond in the same way to the drug.

The joint study of the arthritic diseases is the fourth major collaborative undertaking in the health sciences between the U.S. and U.S.S.R. Earlier agreements include vascular diseases, cancer, and environmental health.

#

News Feature

ACUPUNCTURE'S PAIN-KILLING EFFECT BLOCKED BY MORPHINE ANTAGONIST

Western theories of the mechanism of pain control by acupuncture can be classified as primarily psychological or neurological. Acupuncture has been likened psychologically either to hypnosis or the placebo effect attributable to a patient's confidence in a procedure. Acupuncture has also been compared to electrical stimulation of specific regions of the brain which, when activated, block pain messages from reaching consciousness, and to the pain relieving effects of narcotics which also seem to activate these same pain-inhibiting regions of the brain.

Recent research indicates that acupuncture may fit the pattern of pain control by morphine, because the pain-relieving effects of acupuncture can be reversed by naloxone, a drug that specifically counteracts the effects of narcotic drugs such as morphine and fentanyl. Thus, there appear to be specific regions of the brain with a normal function of inhibiting pain. These regions may be activated by morphine, electrical stimulation, or acupuncture.

Dr. Donald D. Price of the National Institute of Dental Research and Dr. David J. Mayer of the Medical College of Virginia determined the point of pain recognition in groups of volunteers by increasing the stimulation of incisor teeth with an electric vitality tester. A higher pain threshold means that a stronger stimulus is required to evoke pain, and therefore scientists infer that pain relief or a decrease in pain sensibility has occurred.

A group of 35 volunteers received manual acupuncture during a 30-minute

(more)

period. The needles were inserted in the web between the thumb and the forefinger at the HO KU point which controls tooth pain. Because manipulation of the needle is distracting and sometimes painful, it was done for the first two minutes of each five-minute interval between measurements of tooth pain, but not during the tooth test. Individual reactions varied, but the average threshold of pain increased 27 percent, and indicated a small but statistically significant amount of pain reduction.

Another group of 14 subjects was hypnotized and given the suggestion that they would not feel pain. The tooth test showed an average 85 percent increase in pain threshold for these individuals.

During the period of increased pain thresholds, half of the hypnosis group and half of the 20 acupuncture responders were given an injection of naloxone while the remainder of each group received a saline injection. These solutions were given on a double blind basis, neither patient nor doctor knowing what was given at the time. Those subjects in the acupuncture group who received saline had the same elevations of pain thresholds as before. In contrast, when naloxone was given to the other acupuncture subjects, their pain thresholds returned to pre-acupuncture levels. The same experiment, when applied to the hypnosis group, produced different results. Naloxone did not reverse the elevated pain thresholds of any hypnotized subject.

This research shows that at least part of the pain control of acupuncture is attributable to an effect on neural pathways that are also activated by narcotics such as morphine because one chemical antagonist, naloxone, inhibits both. It is possible that acupuncture releases the newly discovered "enkephalin" a pain-killing, morphine-like substance produced by the brain itself.

(more)

These findings also convinced the investigators that hypnosis has a different mechanism than acupuncture, and is a more powerful and predictable method of pain relief.

David J. Mayer, Ph.D., Joseph Barber, Ph.D., and Amir Rafii, M.D., of the Medical College of Virginia, Richmond, and Donald D. Price, Ph.D., of the National Institute of Dental Research, Bethesda, MD, report their findings in the *Proceedings of the International Association for the Study of Pain*, 1976.

#

Photo Feature

TINY TIM, A LEMUR,
IS BORN IN OREGON

Tiny Tim, a one-day-old 70 gram (2.33 Oz.) ring-tailed lemur, peers over the rim of a coffee cup at NIH's Oregon Primate Research Center. A lower form of primate, the lemur is used for genetic and behavioral studies at the Division of Research Resources-supported center in Beaverton, Oregon. (NIH Photo # 1573)

(more)

LEMUR (CONT'D)

Scientists at the Oregon Primate Research Center are finding the ring-tailed lemur *(L. catta)* to be a prime laboratory animal model for genetic studies, especially in the area of twinning.

The ring-tailed lemur is a lower species of primate and has been found to be fairly easy to raise in captivity. The Oregon colony was begun in 1963 with seven ring-tailed lemurs imported from the Malagasy Republic and now numbers 84.

Drs. Richard Van Horn, anthropologist, and Linda Pasztor, geneticist, are conducting physiology and behavior studies with the lemurs at the Center which is supported by NIH's Division of Research Resources. They report that female offspring of twin-bearers invariably produce twins. Six sets of twins have been born in 1976.

A total of 24 female ring-tailed lemurs have had offspring since the colony was started. However, only one-third of them account for all the twins. This leads the researchers to believe that fraternal (not identical) or dizygotic twinning is genetically controlled.

#

News Feature

SEVERITY OF DIARRHEA IN CHOLERA LINKED TO NUTRITIONAL STATUS

Scientists in work funded by the National Institute of Allergy and Infectious Diseases have verified and expanded earlier reports that nutritional status can affect the severity of diarrhea in cholera patients. In a study of hospitalized patients in Dacca, it was found that a 30 to 70 percent increase in diarrhea duration in the more severely malnourished was not related to antibiotic therapy, to intestinal parasites, or to the diet given as the patient recovered. The investigators suggest that poor nutrition retards replacement of normally short-lived intestinal mucosal cells, allowing irreversibly bound cholera toxin to continue to exert an effect.

Malnutrition has long been thought to affect adversely the course of cholera, but no adequate documentation existed. In 1967, a connection between malnutrition and prolonged diarrhea was noted in tetracycline-treated cholera patients, and this was corroborated in 1970.

The present study by Drs. D. L. Palmer, F. T. Koster, A. K. M. J. Alam, and M. R. Islam of the Department of Medicine, Johns Hopkins Center for Medical Research and Training, and the Cholera Research Laboratory, Dacca, Bangladesh, was designed to determine the relationship of protein-calorie malnutrition to severity of cholera in both tetracycline-treated and non-treated patients.

Ninety-seven confirmed cholera patients were entered in the study at the Cholera Research Hospital in Dacca, Bangladesh during the 1974 cholera epidemic, and assigned sequentially to groups which would or would not receive tetracycline. Most of the patients were younger children, typical of groups usually most affected during cholera epidemics. All patients above the median age of eight were considered adults. Because reported ages were unreliable,

(more)

weight-for-height rather than weight-for-age measurements were used to determine nutritional status, comparison data having been obtained from 8,666 normal Bengali children of known age.

The nutritional status of all patients was poor by international standards, though half the children ranged above and half below the Bengali norm. Seventy-eight percent of the children were suffering from first-degree and 17 percent from second-degree malnutrition, which affected 69 and 26 percent of the adults respectively.

Depending on its severity, malnutrition was found to be associated with a 30 to 70 percent increase in duration of diarrhea in all age groups. The effect on volume of stool loss was less pronounced than on duration. Both duration and volume were significantly decreased with tetracycline therapy.

The investigators examined various factors other than malnutrition as causes for the prolonged diarrhea, but found no support for any of these.

Intestinal mucosal cells, which usually have very brief lives, are known to be replaced slowly in diseases of severe malnutrition. The effect of cholera toxin is believed to persist for the life-span of the mucosal cell to which it binds, and this slowed replacement rate could prolong the toxin's effect. The protracted course of cholera in the malnourished is of great significance, since it increases the demand on the hospital for fluids, medical supplies, and nursing care, and adds to the cycle of malnutrition-leading-to-diarrhea-leading-to-malnutrition so prevalent in underdeveloped countries, the investigators say.

A report of the study was published in the *Journal of Infectious Diseases*.

#

News Feature

CHILDHOOD MALNUTRITION AFFECTS LEARNING, MOTIVATION, AND ATTENTION SPAN

Children who do not get enough to eat, in addition to being smaller and sick more often than better-fed children, may also be less able to learn, according to a new publication of the National Institute of Child Health and Human Development(NICHD). *Malnutrition, Learning and Behavior* brings together findings of recent research on the relationship of severe malnutrition and chronic undernutrition to learning and behavior.

Severe malnutrition affects one to two percent of the world's children, many of whom die during the first few years of life. A far greater number, up to half the children of the world, suffer from chronic undernutrition, probably mankind's most pervasive health problem.

According to the new publication, severe malnutrition is rare in the United States, but chronic undernutrition, resulting in poor growth, is more common, especially among poor families. Iron deficiency, on the other hand, is an exception to the established observation that malnutrition is usually associated with poverty; it is found frequently among children of all socio-economic classes.

Recent studies outlined in the publication indicate that prolonged severe malnutrition during gestation and early infancy, when the brain undergoes a rapid growth spurt, brings about specific and often irreversible effects on motivation, attention span and arousal. Severely malnourished babies tend to develop into children with motor insufficiencies and some as yet undefinded retardation in sensory integration.

The effects of moderate or chronic undernutrition are not as clearly

(more)

understood. However, a number of studies show that chronically undernourished children tend to lag in behavioral development, primarily in motor-integrative performance, reading ability, concentration and motivation. Studies in Guatemala, supported by the NICHD, show that children whose malnourished mothers accepted nutritional supplementation in pregnancy were larger at birth, and, by early childhood, did better in behavioral test scores involving motor and manipulative skills than children born of unsupplemented but otherwise comparable mothers. Other intervention studies show that supplementation, starting in pregnancy and continuing through early childhood, resulted in physically more active children.

As the publication states, malnutrition is intimately intertwined with environment, and a cycle is created in which succeeding generations of children are often caught and hopelessly revolve. Undernourished mothers bear babies who are also undernourished and underweight. The quantity of breast milk and the duration of breastfeeding are reduced. The mother is inactive and plays little with her baby, who is timid, passive, and undemanding, and becomes a child with little energy, listless, and accustomed to meager food supplies. In school he is lost, discouraged, inattentive--a child with learning difficulties.

The NICHD offers this booklet to focus the attention of health workers and teachers on the effects of hunger and malnutrition on the development of children, the extent to which they are temporarily or permanently handicapped in learning, and the possibilities of rehabilitation.

Single free copies are available on request from the NICHD Office of Research Reporting, NIH,Bethesda, Maryland 20014. Telephone (301) 496-5133.

#

NOTICE TO MEDICAL AND DENTAL STUDENTS

Applications are now being accepted for Clinical, Research, and Staff Associate appointments at the National Institutes of Health in Bethesda, Maryland.

The Associateships are two-year appointments offering training and experience in clinical and laboratory investigation. Young physicians and dentists from most of the health specialties and basic biomedical sciences are eligible. Candidates may apply during their third or fourth year of medical school or while in intern or residency training. Most Associates begin their tour of duty after completing two years of postdoctoral training.

Most appointments will begin July 1979; however, a few positions are available for July 1978.

The deadline for receipt of applications is February 15, 1977. Interviews will be conducted April 18-29, 1977. Final selections will be made in May by a matching process similar to that of the National Intern and Resident Matching Program.

Request application packets by writing to: NIH Associate Program, National Institutes of Health, Building 10, Room 1N-238A, Bethesda, Maryland 20014.

#

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Ms. Joyce Flaherty
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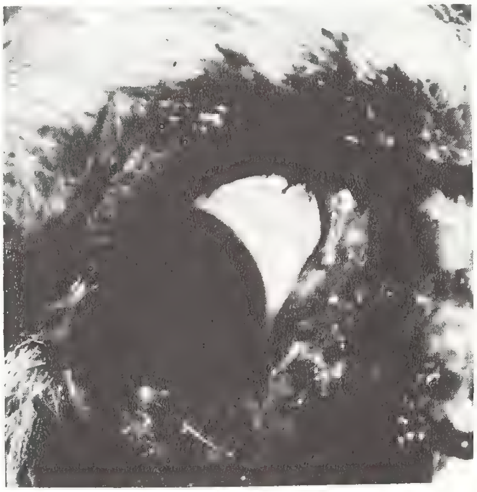

See page 11

RESEARCH ADVANCES:

Texans Study Effect of Pineal Gland on Biorhythm..1
Therapies Evaluated for Gonococcal Arthritis.......3
Possible Clue Seen to Cause of Miscarriages............5
Pretreatment with Drug Helps Mice Survive Malaria Strain....................8

NEWS AND PHOTO FEATURES:

Cancer Scientists Use Immunotherapy in Bovine Squamous Cell Carcinoma..11
Two Human Livers Are Stored, Transported, and Transplanted..15
Cell Fusion Technique Is Used to Study Hemoglobin Disorders.19
Drug May Help Patients After Gastric Surgery...............23
U.S. and Japan Agree to Do Research into Eye Diseases.......25
Ear Acupuncture for Obesity Is Questioned..................28

NOTE TO THE MEDIA:

NIH to Hold Science Writers Seminar on Chromatin and Protein Synthesis..30

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Research Advances

TEXANS STUDY EFFECT OF PINEAL GLAND ON BIORHYTHM

Located in the center of the brain and sometimes identified as the "third eye" in Eastern religions, the pineal gland has been shown by University of Texas researchers to have a distinct effect upon the regulation of circadian (24 hour) biorhythm. Their research, supported by the NIH's National Institute of Child Health and Human Development, offers evidence that variations in the dosage of a particular pineal hormone, melatonin, alters the 24-hour activity-rest cycle in sparrows.

Previous investigation had demonstrated that removal of the sparrows pineal gland abolishes the circadian biorhythm, and that its replacement restored rhythmicity. However, when the gland was not removed but denervated, circadian biorhythm was maintained, indicating that the pineal organ is coupled with other components of the circadian system by hormones rather than nerves. The results of this research strongly suggests that melatonin is that coupling hormonal messenger or regulator.

Thirty-seven house sparrows (Passer domesticus) were captured near Austin, Texas, moved indoors and held individually in light-tight cages. The period of locomotor (perch hopping) activity was recorded throughout the study for each bird. The activity rhythm was determined by measuring the time interval between the onset of perch hopping on successive days.

The sparrows were initially maintained for three to four weeks on a light-dark cycle of 12:12 (12 hours of light per day) and then for at least three weeks were kept in total darkness.

After this period, 30 of the birds had a capsule containing melatonin

(more)

placed in their abdomen. The capsules were made of a special material (silastic) which slowly released melatonin into their systems. The capsules varied in length from two to 10mm and the amount of melatonin released was determined by weighing them before implantation and after removal. Seven of the sparrows received empty capsules and all the birds were returned to total darkness.

Of the 30 birds receiving the melatonin capsules, ten had shortened activity periods, and 16 went into constant activity. These reactions are similar to the behavior of sparrows exposed to constant bright light, which induces constant activity, and sparrows exposed to constant dim light, which causes shortened activity periods.

When the capsules were removed, the birds reverted to normal circadian biorhythm. The seven birds receiving empty capsules never displayed any changes in activity. The relationship between melatonin dosages and either shortened or constant locomotor activity is still being clarified.

Further investigation is indicated to discover the site of action of melatonin and its possible interaction with other agents, notably light, which affect circadian biorhythm. Nevertheless, this research demonstrates that a naturally occurring substance, melatonin, can produce profound effects upon the major parameter of circadian biorhythm, the activity cycle.

These findings were reported by Drs. Fred Turek, Joseph P. McMillan, and Michael Menaker in the December 24, 1976 issue of *Science*.

#

Research Advances

THERAPIES EVALUATED FOR GONOCOCCAL ARTHRITIS

Grantees of the National Institute of Arthritis, Metabolism, and Digestive Diseases have completed a trial comparing low-dose intramuscular versus high-dose intravenous penicillin therapy for gonococcal arthritis.

A total of 63 patients completed the trial, with 36 assigned to the low-dose regimen (600,000 units of procaine penicillin G given intramuscularly every 12 hours for ten days) and 27 to the high-dose therapy (aqueous penicillin G, 10 million units daily, infused continuously for the first three days in addition to the intramuscular procaine penicillin regimen). No significant therapeutic difference was found in the response of the two groups.

Gonococcal arthritis is the most common and disabling complication of untreated gonorrhea. Generally the onset is sudden, occurring one to four weeks after initial infection, and causing acute arthritic inflammation of the knees, wrists and ankles. However, the onset may be delayed for months or years when pregnancy or pelvic surgery cause a latent infection to flare up.

The course of gonococcal arthritis is extremely variable, ranging from complete recovery after several weeks, to permanent severe limitation of motion in the afflicted joints, particularly the smaller joints of the wrists and the hands.

In addition to penicillin therapy, the treatment of gonococcal arthritis consists of bed rest until fever decreases and immobilization of the involved joints until inflammation subsides.

The patients in this trial were admitted to the City of Memphis Hospital

(more)

between September 1972 and September 1975 with an initial diagnosis of gonococcal arthritis. They were divided by double-blind random number assignment to low-and-high dose regimens within 24 hours of admission. Before initiating therapy, cultures were taken to assure that the causative agent of infection was *Neissera gonorrhoeae.*

Each patient was examined daily by the same physician who had no knowledge of the therapy. The peak daily temperature was noted, and all involved joints were graded for heat, tenderness, range of motion, and pain. The circumference of each involved medium or large joint was also measured daily. When the pretreatment symptoms and laboratory findings of the 63 patients involved in the study were analyzed, no significant variables were found between the 36 low-dose and 27 high-dose patients.

The therapeutic response between the two groups was compared in terms of the percentage of patients requiring anti-inflammatory or analgesic agents, the number of days until the involved joints were fever and pain-free with full range of motion restored, and the number of days of therapy in the hospital. No significant difference was found.

Drs. David E. Trentham, John W. McCravey, and Alfonso T. Masi, of the University of Tennessee Center for the Health Sciences reported their findings in the November 22, 1976, issue of the *Journal of the American Medical Association.*

Some of the beneficial implications of this trial are that low-dose intramuscular penicillin therapy is less expensive than the high-dose intravenous regimen, causes less patient discomfort and immobility, and reduces the danger of dosage error or in-hospital infection.

#

Research Advances

POSSIBLE CLUE SEEN TO CAUSE OF MISCARRIAGES

Boston investigators, partially supported by the National Institute of Allergy and Infectious Diseases, have reported that an immunologic "blocking factor" -- normally present in maternal blood serum -- is absent from sera of women who chronically abort. This observation may help explain why certain women have recurrent miscarriages.

One of the unresolved enigmas in immunology is why the uterus, in a normal pregnancy, provides an immunological "retreat" for the fetus, where, though possessing "foreign" antigens from the father, it is protected against the threat of rejection. Several theories have been proposed to explain this phenomenon. One, explored by the researchers in the present study, has suggested that the mother's immunologic reactivity (similar to responses involved in graft rejection) may be modified by a substance in her serum.

According to previous work done by the investigators, a woman's lymphocytes -- specific immune defense cells -- become sensitized to fetal/paternal antigens after several pregnancies, producing a cellular immune response that increases with each pregnancy. The laboratory measurement of this response is the production of a substance by the lymphocytes -- migration inhibitory factor (MIF) -- that inhibits the migration of guinea pig macrophages in a capillary tube.

In the present study, the specific immune response, MIF production, of eight women with three or more previous miscarriages to their mates was measured. In addition, eight women similar to the patient group with one exception -- each had two or more normal pregnancies -- were chosen as the

(more)

MISCARRIAGES (CONT'D)

controls.

After blood samples were taken, each woman's lymphocytes were mixed with cells acting as antigens from her mate and divided into two groups. One culture was incubated in the woman's serum and the other in the serum from another woman (foreign serum). The researchers found that, in the presence of foreign serum, lymphocytes from seven out of eight women in the control group produced MIF to their mate's antigens -- as did the lymphocytes from all the woman who had chronic miscarriages. But, the researchers also found that, in the presence of their own serum, lymphocytes from the control group failed to produce any MIF, indicating the existence of a factor in a normal woman's sera that blocks the immune response to her mate. In direct contrast, no blocking activity was detected in the sera of women who had frequent miscarriages.

Based on these findings, the researchers hypothesized that blocking factor is biologically significant in the development of normal pregnancy. In an additional case, a woman with three miscarriages and a successful fourth pregnancy provided even more convincing evidence. At the time of two of the miscarriages, this woman's sera was tested and found to lack blocking factor. However, in her fourth pregnancy, blocking activity was detected in the third trimester and after childbirth.

Blocking factor, according to tests performed by the investigators, is an IgG antibody -- the major class of antibodies in human serum. How the antibody blocks lymphocyte response is still unknown, but the scientists suggest that it may "cover up" a specific paternal antigen by attaching to its surface, thus preventing lymphocyte recognition.

(more)

MISCARRIAGES (CONT'D)

The researchers are also interested in finding out why blocking factor does not develop in women with chronic miscarriages. One explanation currently under investigation, is that shared histocompatibility antigens, genetically determined substances that influence an individual's immune response between a husband and wife, may result in sufficient immunological stimulation for the production of blocking factor.

The scientists point out that their studies do not totally disprove the possibility that blocking factor may develop as a result of pregnancies carried to term rather than being necessary to prevent miscarriage. To resolve this issue, they recommend that many more pregnancies be followed. Studies are currently under way to determine when blocking factor appears in initial and subsequent pregnancies in normal women.

As the next step in their research, the investigators plan to extract antibody from the placentas of women with normal pregnancies and from those with chronic miscarriages to determine the presence of blocking activity in fetal material -- a finding that may further substantiate the role of blocking factor in normal pregnancy.

The report of this research by Ross E. Rocklin, John L. Kitzmiller, Charles B. Carpenter, Marvin R. Garovoy and John R. David from the departments of Medicine and Obstetrics and Gynecology at the Harvard Medical School, Robert B. Brigham Hospital, Boston Hospital for Women and Peter Bent Brigham Hospital, appeared in the November 25, 1976 issue of the *New England of Medicine*.

#

Research Advances

PRETREATMENT WITH DRUG HELPS MICE SURVIVE MALARIA STRAIN

Pretreatment with the drug cyclophosphamide (Cy) enables mice to survive subsequent infection with a lethal strain of malaria, according to a recent report by Dr. John Finerty of the National Institute of Allergy and Infectious Diseases Laboratory of Microbial Immunity, and Dr. Edward Krehl of Trudeau Institute, Saranac Lake, N.Y.

This protection appears to result from the drug's enhancement of the activity of T cells, the thymus-dependent lymphocytes that mediate cellular immune responses.

The effect of cyclophosphamide on the immune system apparently varies with its time of administration. If given simultaneously with infectious organisms or after an infection is established, Cy is a potent suppressor of the immune response. However, several studies have shown that Cy can increase the immune response to certain nonviable antigens if administered prior to immunization with them.

To determine the effects of Cy on the immune response to malaria parasites, the researchers administered the drug to mice 48 hours before infecting them with a lethal strain of malaria, *Plasmodium berghei yoelli* 17XL. At various times during an infection, the presence of delayed hypersensitivity, an indication of T cell activity, was determined by injecting the animal's footpad with a challenge dose of malaria antigen and then measuring any increase in the thickness of the footpad.

Mice pretreated with Cy exhibited a delayed hypersensitivity (DH) response which peaked at day two of infection but decreased sharply on day

(more)

four. These animals, however, overcame the lethal infection, unlike a group of similarly infected mice which had not received Cy. The DH response of the untreated animals did not peak until day six, shortly before their deaths.

Drs. Finerty and Krehl next examined the relationship between the DH response and the level of parasites in the blood of Cy treated and untreated mice infected with the same lethal organisms. They found parasites in the blood of the Cy mice from day two, although the numbers did not increase until day four, peaked at day 11, and disappeared by day 24. Thus, the low level of parasitemia coincided with the high DH response seen in Cy mice; likewise, the subsequent increase in parasitemia coincided with the decrease in DH. In contrast, the level of parasitemia in a non-Cy group of mice rose sharply from day two until their deaths on day nine, paralleling the weak DH response observed in other non-Cy mice.

These results suggest that T cells may play a vital role early in malaria infection. The scientists feel, therefore, that pretreatment with cyclophosphamide enhanced the T cell reactivity and was responsible, in part, for protecting the mice against the lethal infection.

They point out, however, that the mechanism whereby Cy alters the immune response, either by suppression or enhancement, are still not understood. Thus, it is possible that pretreatment with cyclophosphamide could have suppressed the response of B cells, anitbody-producing lymphocytes. Such antibody may interfere with the development of immunity to parasites. Studies are now underway to investigate the mechanisms involved.

These findings, reported in the October, 1976 issue of *Infection and Immunity*, also indicate that host immunity can be manipulated by chemical

(more)

MALARIA (CONT'D)

agents in a situation in which protective means of immunization do not exist. This also represents the first demonstration of delayed hypersensitivity in malaria.

#

ENDOCRINOLOGY--Endocrinology, the study of the internal glandular secretions of the body, is an immense biomedical field which directly pertains to important life functions, such as growth, metabolism, and reproduction, according to the National Institutes of Health.

SIDS--The sudden infant death syndrome (SIDS) is the leading cause of death in infants after the first month of life, claiming the lives of three infants for every thousand live births, according to the National Institutes of Health.

FOOD ALLERGIES--The most common food allergies are to fish, berries, nuts, eggs, cereals, milk, pork, chocolate, beans, and various fresh fruits. The National Institutes of Health reports that some people are also allergic to such substances as food additives.

Photo Feature

CANCER SCIENTISTS USE IMMUNOTHERAPY IN BOVINE SQUAMOUS CELL CARCINOMA

Bovine "cancer eye," a naturally occurring cancer in cattle, can be treated successfully with a substance that stimulates the cow's immune defense system, according to Drs. Herbert J. Rapp, Laboratory of Immunobiology, National Cancer Institute, and Stephen J. Kleinschuster, Department of Anatomy, Colorado State University, Fort Collins. This conclusion is based on research that they are doing with Drs. David C. Leuker and Robert A. Kainer, also of Colorado State, and that was reported in New York City at an International Conference on Immunobiology of Cancer.

"Cancer eye" is classified as a squamous cell carcinoma, a type of cancer that is found frequently in human cancers of the lung, mouth, esophagus and skin. The effective use of immune stimulation (immunotherapy) may point the way toward a valuable approach for the treatment of cancer patients.

"Cancer eye" is rarely seen in cattle before they are three years old, and occurs most often at about eight years of age. The cancer develops on the cornea (the clear part of the eye covering the pupil), the sclera (the white membrane covering the eyeball from the iris back), the nictitating membrane (a membrane that folds into the inner corner of the eye), or the lower eyelid.

In conventional treatment, the cancer and surrounding tissue are removed by surgery. This approach has not been very effective, however. If untreated, the cancer will metastasize (spread) through the circulatory system, and the animal eventually will have to be destroyed.

The scientists used a preparation of BCG (bacillus Calmette-Guerin), a strain of bacteria studied extensively by immunologists in attempts to stimu-

(more)

late the body's immune system to "reject" growing cancers. The preparation used to treat bovine "cancer eye" consisted of bacterial cell walls suspended in mineral oil droplets that were in turn mixed with water in an emulsion.

Hereford cattle were obtained from local ranches. The diagnosis of cancer was made by studying a tissue specimen under the microscope. Once the diagnosis of bovine ocular squamous cell carcinoma ("cancer eye") had been established, the animals were divided into three groups. The study group received the BCG vaccine; the control group received a vaccine in which the BCG cell walls were suspended in water instead of the oil droplets; and the third group received a single injection of vaccine directly into the tumor.

A total of 42 cattle were used in the research. Of the 24 animals in the study group, 17 (71 percent) responded to the treatment. At the time of the report, seven of them were free of visible cancer, two others had cancers in the process of shrinking, and eight had cancers whose growth had halted. Photos 1 through 4 show the progressive disappearance of cancer in one of the treated animals. The sequence took place over a period of about four weeks.

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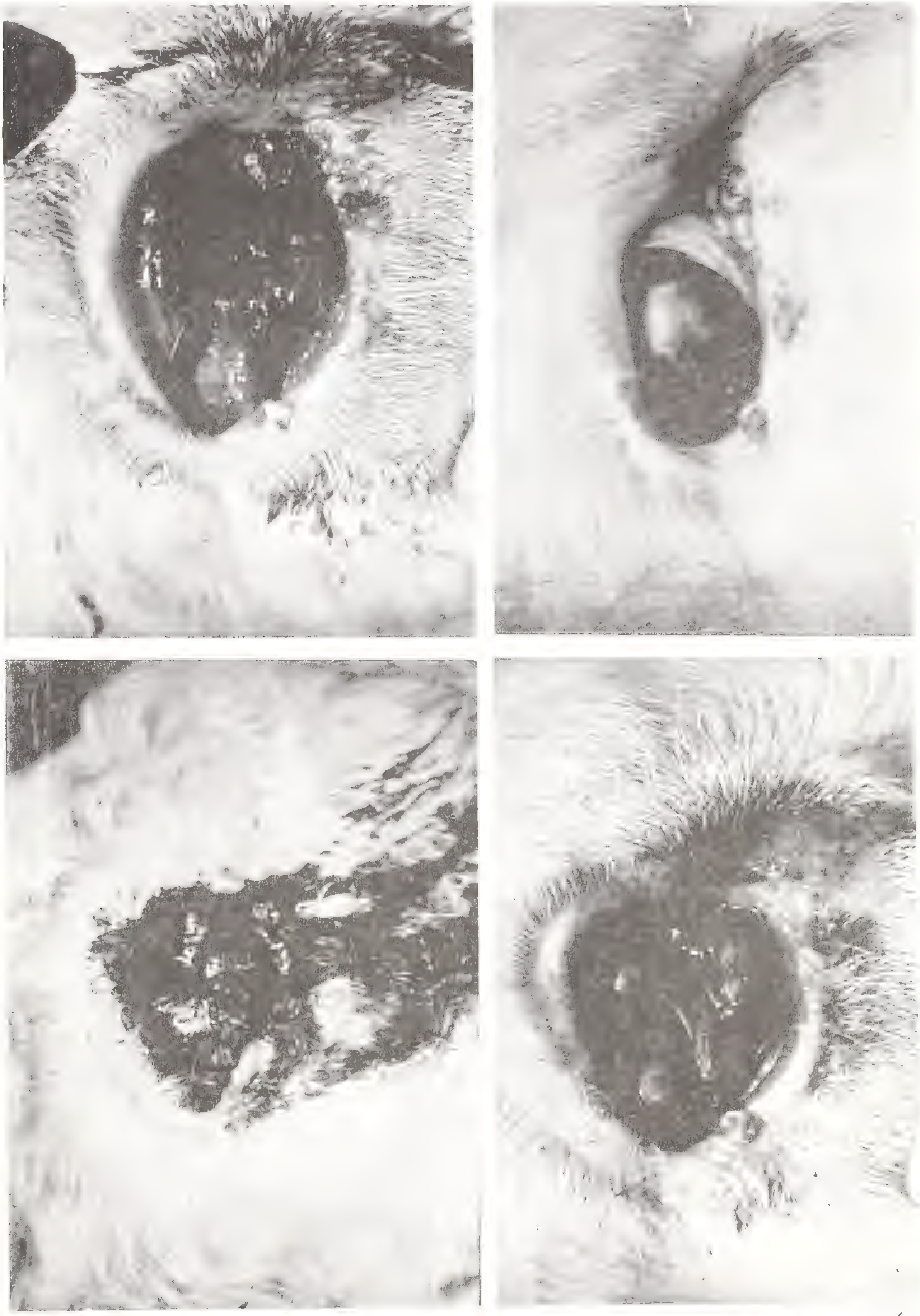

Photos 1 through 4

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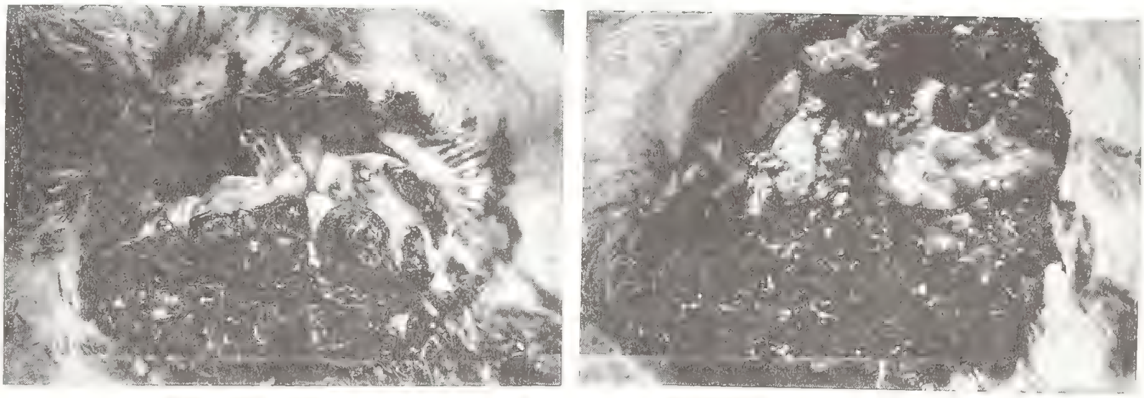
BOVINE CARCINOMA (CONT'D)

Cancer continued to grow in all of the animals in the control and untreated groups. *(See below)*



The implications of this experiment go beyond demonstrating that there may be a better method than surgery for treating bovine "cancer eye." Immunotherapy of cancer in humans, too, may benefit eventually from this work.

Animal models for the immunotherapy of cancer have had little direct bearing on the treatment of human cancer, the scientists believe. These other experiments have involved specially bred, small rodents with non-metastasizing cancers that have been induced or transplanted. A far more satisfactory guide for the treatment of cancer would be a large, random-breeding animal in which the cancer occurs naturally and spreads beyond the initial location. "Cancer eye" in cattle may well be the guide that will help establish a role for immunotherapy in the treatment of similar human cancers.

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News Feature

TWO HUMAN LIVERS ARE STORED, TRANSPORTED, AND TRANSPLANTED

University of Colorado Medical Center surgeons, using a special clinical research unit supported by NIH's Division of Research Resources, have successfully transplanted two livers removed from donors in Los Angeles and flown to Denver. The two procedures mark the first time in the United States that livers have been stored for long periods of time and transported lengthy distances before transplantation.

According to the Colorado surgeons, the ability to store and ship livers before transplanting them overcomes at an early stage the potential problem of donor organ shortages should the currently experimental liver transplant operation become common in future years. Such shortages have hampered kidney transplant efforts in recent years.

On November 11, a liver was removed at the UCLA Medical Center and, after a two-hour plane trip, was transplanted in a seven-year-old girl suffering from what would have been a fatal congenital liver disease. Earlier, on September 1, a liver was removed at Los Angeles Children's Hospital and later implanted in a two and one-half-old boy with biliary cirrhosis, which would have resulted in death for the child.

According to University doctors, the first patient has left the hospital and is "doing fine." The latest patient is in satisfactory condition at the University of Colorado Medical Center (as of December 2).

During the critical periods, just before and following the transplants, the surgical team hospitalized the recipients on a special patient-centered hospital research unit called a clinical research center. One of 82 such

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centers supported by the Division of Research Resources at medical institutions throughout the United States, this miniature research hospital within the larger hospital provides highly specialized clinical research facilities to the entire Colorado medical center staff.

According to Dr. Thomas E. Starzl, who heads up the transplantation team, the technique of preserving and transporting a liver is similar to that used in moving kidneys over long distances. The process involves cold-storage and maintaining the tissue hydration of the organ in an electrolyte solution. This is accomplished by storing the liver in an environment-controlled styrofoam chest transported under physician supervision in the passenger section of a commercial airliner.

"We always thought of the liver as much more fragile than the kidney," Dr. Starzl explains. "We just didn't think it would be possible to transport and preserve it for long periods of time. We did some experimental work in our lab with liver transplantation between animals and found that we could keep a liver usable for 12 to 14 hours. We then decided to try human transplants."

Dr. Charles Putnam, another member of the surgical team, reports the two human transplantation efforts took seven to eight hours from the time the liver was removed from the donor to its successful transplantation. Drs. Charles Halgrimson, Joseph Benichou, and other members of the Colorado team, coordinated by Paul Taylor, flew to Los Angeles to remove the livers and then flew back to Denver with the organs to perform the implant procedures. Dr. Putnam explains the removal and implant procedures were carefully coordinated with commercial airline schedules between the two cities.

(more)

The California donors were matched with the Colorado recipients through the efforts of professional donor coordinators in Denver and Los Angeles.

The University of Colorado surgeons now have performed 116 liver transplants, more than any other medical group in the world. According to the Colorado doctors, the procedure is still experimental because the results are not yet predictable.

"This is one reason why we hospitalize all liver transplant recipients on the Division of Research Resources-funded clinical research center. . . so we can learn as much as possible from each patient," Dr. Putnam says. "The facilities of the center and the personnel working on the unit are best suited to manage patients who require unusual care and who, at the same time, are being studied from a research point-of-view.

"The clinical research center gives us access to highly reliable and sophisticated laboratories which are critical for liver transplant cases. The unit also allows us to work with nurses who provide extremely competent care and, at the same time, are used to working under strict research protocols

Of the 116 liver recipients, 30 lived at least one year post-operatively, 14 are still alive, and the longest survivor is approaching seven years.

"The survival rate is not good enough yet to make the procedure a standard clinical tool," Dr. Putnam says. "The results must improve to take it out of the experimental stage."

Dr. Starzl says even though the operation is still considered experimental, increased feasibility of the procedure makes it necessary to expand organ availability.

"The success of organ storage and shipment that we have been able to

(more)

LIVERS (CONT'D)

accomplish overcomes a tremendous logistical barrier to increased liver transplantation," he says. "Many patients have benefited from the procedure. There is little reason to doubt that liver replacement will be a more common operation in the years to come. A shortage of organs may then present an obstacle, as it has with kidney transplants. The ability to store and ship organs is a large step in overcoming this potential problem."

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December 1976

NEWS & FEATURES From NIH

News Feature

CELL FUSION TECHNIQUE IS USED TO STUDY HEMOGLOBIN DISORDERS

In their research on Cooley's anemia, sickle cell anemia, and other hereditary disorders affecting the production of hemoglobin by red blood cells, National Heart, Lung, and Blood Institute (NHLBI) scientists are using a powerful new technique called cell fusion. The research is being performed by Drs. Albert Deisseroth, A. W. Nienhuis, W.F. Anderson, Raymond Velez, Jane Barber, Judith Kantor, Alan Steggles, and Golder Wilson.

The fusion of hemoglobin-producing cells from different species (mouse and human, hamster and human, etc.) results in hybrid cells containing various mixes of the genetic material originally present in both parent cells. This material, DNA, is carried by genes located on structures called chromosomes in the cell nucleus. In some of these "matings" many of the normal human complement of 24 chromosomes are excluded from the resulting hybrid.

In fact, the fusions of mouse and human erythroid cells has yielded some hybrid strains containing only a single human chromosome in company with a full complement of mouse chromosomes. The single human chromosome incorporated may vary from one hybrid strain to the next; but the fusion technique effectively isolates that chromosome for studies of what genes it carries, their locations on the chromosome, or how the genetic blueprints carried by the DNA of the genes are translated (via RNA) into the structural proteins, enzymes, and other substances produced in the cell. Cooley's anemia, also called beta thalassemia, is a serious hereditary hemoglobin disorder that affects chiefly Greeks, Italians, and other Mediterranean peoples and their descendants. The thalassemias comprise a family of diseases whose prevalence in the U.S. is not known with

(more)

certainty, but worldwide, these genetic defects are very common and the severe forms of the thalassemias are a major health problem.

Earlier NHLBI studies disclosed the genetic defect underlying Cooley's anemia. In the normal synthesis of hemoglobin (the oxygen-carrying substance of the red blood cell or its precursors), eight "sub-units" are required. Four of these are molecules of an iron-containing substance called heme. Assembled in the proper alignment the four heme molecules act as the prosthetic group, or "business end" of hemoglobin. The other four components are protein chains called globins. Two are identical proteins called alpha chains; the other two are identical proteins called beta chains. Alpha and beta chains differ from each other in molecular weight and also in the amino-acid sequence of their respective chains.

Normally, alpha and beta chains are synthesized at the same rates by hemoglobin-producing cells. In Cooley's anemia, alpha chains are produced at the normal rate, but beta chain production is abnormally slow. As a result, excess alpha chains pile up in the red blood cell, then precipitate, "crippling" the red blood cell and causing it to be destroyed long before it has lived out its allotted span. This is the basis of the anemia that can now be corrected only by periodic transfusions.

The NHLBI studies established that the subnormal production of beta chains was due to a scarcity of beta globin messenger RNA (beta-mRNA). Produced by DNA in the nucleus, beta-mRNA carries the "blueprint" for the assembly of the beta chain. The limited amount of beta-mRNA in the cells from patients with Cooley's anemia is structurally normal, the NHLBI studies showed, and so are the beta chains synthesized by the beta-mRNA. There is simply too little

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beta-mRNA to keep pace with the production of alpha chains by alpha-mRNA.

The basic flaw of Cooley's anemia, then, appears to be faulty regulation in the synthesis of a gene product. Cell-fusion techniques offer a promising means of zeroing in on mechanisms involved in globin-mRNA synthesis by DNA and on factors that may stimulate or inhibit mRNA output in red-cell precursors and thereby affect hemoglobin synthesis in the circulating red blood cell.

Studies thus far with mouse/human erythroid hybrids have yielded strains that 1) produced neither mouse nor human globins; 2) produced mouse, but not human globins; 3) produced mouse globins and human beta-chain globin, but not human alpha globin. This last hybrid indicates that the genes producing alpha and beta globin mRNA are located on different human chromosomes.

Certain of the hybrid cells have been shown to contain both mouse and human globin genes, but these genes are not expressed in mRNA production or hemoglobin synthesis. Thus regulatory factors are operative in these hybrid cells.

The human erythroid cell contains a number of bi-armed chromosomes, and it appears that two of these carry the genes for alpha and beta globin mRNA since expression of the human globin genes has only occurred in hybrid cells which contain at least two or three human bi-armed chromosomes.

Continued research on the genetic flaw in Cooley's anemia may lead to treatment methods more direct and effective than periodic transfusions. Transfusion temporarily restores the oxygen-carrying capacity of the blood of patients with Cooley's anemia; but the continuous destruction of beta-globin deficient cells and reduced life of transfused red cells result in the accumu-

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lation in various tissues of excessive iron, a condition called hemosiderosis. The effects vary from one tissue to the next. but hemosiderosis is a leading cause of disability and death in Cooley's anemia. Chelating agents, which combine with iron to form complexes more readily excreted by the kidneys, hold promise for the treatment of hemosiderosis, but results thus far have been only modestly successful.

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News Feature

DRUG MAY HELP PATIENTS AFTER GASTRIC SURGERY

California scientists whose work is supported by the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD) have shown that metoclopramide, an investigational drug which stimulates gastric motility, may be of value in treating the chronically-impaired gastric emptying which often follows gastric surgery.

Gastric emptying is impaired during the first few months after vagotomy and antrectomy even in asymptomatic patients. Surgical remedies, such as anastomotic revisions, often fail, and current medical approaches such as nasogastric suction, cholinergic drug therapy, and various diets are of dubious effectiveness.

The present research indicates that metoclopramide may be useful. Intramuscular metoclopramide produced a 2.6-fold increase in gastric emptying 90 minutes after eating a meal and was without untoward effects.

Six patients with chronic gastric retention who had undergone vagotomy, gastric resection, and anastomotic revision, and eight normal volunteer subjects were studied. The former received 10 mg metoclopramide, or placebo, intramuscularly, in a double blind fashion before meals and at bedtime for three days. Gastric emptying was measured using a gamma camera technique and a solid meal labeled with ^{99}mTc-DTPA. Normal subjects underwent similar studies.

In normal subjects, after placebo, 64.3 percent of the isotope remained in the stomach 90 minutes after a meal; after metoclopramide, 59.1 percent remained,

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a difference that was not significant. In postsurgical patients, however, after placebo, 82.6 percent of the isotope remained at 90 minutes, while only 54.7 percent remained after metoclopramide. This represents a 2.6-fold increase in emptying, which in symptomatic patients was associated with less nausea, vomiting and bloating.

Although much has been learned about metoclopramide's effect on gastric motility in man during the past decade, its precise mechanisms of action are still poorly understood. Dr. William H. Metzger and associates of the VA Hospital Center and the University of California, Los Angeles, supported by a NIAMDD grant to the UCLA Center for Ulcer Research and Education, reported their study in *Gastroenterology*.

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News Feature

U.S. AND JAPAN AGREE TO DO RESEARCH INTO EYE DISEASES

An agreement between the United States and Japan to further research on blinding and disabling eye diseases through exchange of scientists was announced in December by Assistant Secretary for Health, Theodore Cooper, M.D., and Dr. Seiji Kaya, President, Japan Society for the Promotion of Science.

Under terms of the Memorandum of Understanding, laboratory and clinical investigators of both countries will collaborate in important areas of vision research. This is the first formal agreement for such an exchange between the U.S. and any foreign country.

The intent of the U.S. - Japan Agreement is to foster better utilization of existing resources for vision research in both countries, with a resulting exchange of ideas and approaches on health problems common to both nations.

Signing the Memorandum of Understanding for the U.S., Carl Kupfer, M.D., Director of HEW's National Eye Institute (NEI) said, "I am eagerly looking forward to this collaboration with the Japanese vision research community which has established an international reputation in such key scientific areas as visual pigment, neurophysiology, tissue culture and corneal transplantation. In turn, we have much to offer the Japanese scientists in the areas of ophthalmic biochemistry, physiology, pathology and clinical trials." Masao Yoshiki, M.D., Director General of the Japan Society for the Promotion of Science, signed the Memorandum on behalf of his country.

Initially covering a three-year period, the Memorandum of Understanding will be reviewed at the end of that time, after which it will remain in force until either country decides to terminate it.

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EYE (CONT'D)

In the first three-year period, two scientists per year from each country will be selected for the exchange. One laboratory or clinical investigator will be on short-term exchange not to exceed four months; the second will participate for not less than three months but no longer than 12 months. Interested scientists in both the United States and Japan will select a research area in which they wish to work and then make tentative arrangements to collaborate with an investigator of their choice. Selections from this group will be made by a review panel in the scientist's own country, after which the names of the Japanese scientists will be submitted to the Director of the NEI for consideration. In turn, the U.S. panel's selection will be considered by the Director General of the Japan Society for the Promotion of Science.

The first U.S. participant, Hitoshi Shichi, Ph.D., of NEI's Laboratory of Vision Research, spent approximately four months working in the Laboratory of Professor Toru Yoshizawa with Professors Tokindo Okada and Goro Eguchi at Kyoto University, Kyoto, Japan. The area of research of the three scientists involved studies on rhodopsin, the photosensitive pigment of the rod cells of the retina and a key element in transforming light energy into visual impulses.

Professor Toru Yoshizawa, Japan's first exchange scientist, will spend three months working with investigators at Princeton University; Bell Laboratories, Princeton, New Jersey; University of Illinois, Chicago; and Amherst College, Amherst, Massachusetts. His field of interest is photobiology and sensory physiology.

Selected to collaborate with U.S. scientists for a one-year period is Makoto Tamai, Assistant Professor, Department of Ophthalmology, Tohoku University

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EYE (CONT'D)

School of Medicine, Sendai, Japan. His area of research is the morphology and function of the vertebrate retina. Dr. Tamai will spend the major part of the year working with members of the NEI staff.

A bilateral research effort in the biomedical sciences has been in effect between the U.S. and Japan since 1965. This agreement concerns major health problems in many Asian countries, including the control and prevention of cholera, leprosy, malnutrition, parasitic disease, and now, vision research. Additionally, the National Cancer Institute has a collaborative program in Career Research with the Japan Society for the Promotion of Science.

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NEWS & FEATURES From NIH December 1976

News Feature

EAR ACUPUNCTURE FOR OBESITY IS QUESTIONED

A California grantee of the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD) has shown that ear acupuncture for obesity, which has become popular in the United States in recent years, is not associated with any significant weight reduction.

Although use of acupuncture in the treatment of obesity is relatively new, it has spread rapidly in the United States. Weight losses of 20 to 25 percent have been reported, for example, following insertion of surgical staples or acupuncture needles at specific "hunger points" in both ears. However, there have been no controlled and statistically analyzed studies of the efficacy of this procedure.

In the present well-controlled study, similar acupuncture therapy techniques were employed in 24 obese volunteers. At the same time these studies were duplicated in guinea pigs in order to eliminate the possible effects of suggestibility in human patients. In both human and animal subjects no form of ear acupuncture was associated with significant weight loss.

The 24 volunteers, who were five to 33 percent above ideal weight, were weighed before and after a three-week control period and after acupuncture therapy. Acupuncture needles were placed in specific auricular loci, at both hunger points and non-hunger points, both unilaterally and bilaterally, for nine weeks, and in random order for three week periods. The volunteers manipulated the needles for several minutes prior to eating.

Variable subjective responses to the effects of acupuncture on appetite were noted, ranging from no effect to a sensation of early satiety, with

(more)

generally decreased hunger. In addition, the needles were generally well tolerated. There was no statistically significant change in body weight, however, either in the 24 volunteers or in the guinea pigs.

Previous reports of clinical success with ear acupuncture failed to disclose if the patients were simultaneously on a weight reduction diet, the studies lacked control groups, and no tables or statistical analysis of data were provided. It is concluded from the present findings that ear acupuncture has no positive effect on weight loss in the obese.

NIAMDD grantee Dr. George A. Bray of Harbor General Hospital, Torrance, Calif., and associates reported their study in the *American Journal of Clinical Nutrition.*

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NEWS & FEATURES From NIH

December 1976

NOTE TO THE MEDIA

Schedule of NIH Science Writers Seminars, January - June 1977

JANUARY 25, 1977
9:30 a.m. to noon

CHROMATIN[*] AND PROTEIN SYNTHESIS

- Gary Felsenfeld, Ph.D., National Institute of Arthritis, Metabolism, and Digestive Diseases - Organization of DNA in higher organisms and its relationship to biological activity.
- Arthur W. Nienhuis, M.D., National Heart, Lung, and Blood Institute - The genes for hemoglobin: a model for the study of gene regulation.
- Philip Leder, M.D., National Institute of Child Health and Human Development - Organization of antibody genes: a DNA cloning approach.

APRIL 19, 1977
2:00 to 4:30 p.m.

IMMUNOLOGY RESEARCH

- David M. Sachs, M.D., National Cancer Institute - Transplantation biology.
- Ira Green, M.D., National Institute of Allergy and Infectious Diseases - Malignancies of human lymphoid cells.
- Paul H. Levine, M.D., National Cancer Institute - Clinical implications of immunity to virus- and tumor-associated antigens.

JUNE 7, 1977
9:30 a.m. to noon

RESEARCH ON THE GASTROINTESTINAL SYSTEM

- Jerry D. Gardner, M.D., National Institute of Arthritis, Metabolism, and Digestive Diseases - Gastrointestinal hormones.
- Warren Strober, M.D., National Cancer Institute - Immunology of the gastrointestinal tract.
- Paul D. Berk, M.D., National Institute of Arthritis, Metabolism, and Digestive Diseases - New Developments in the treatment of liver diseases.

For program details, call Jane Collins, Seminar Coordinator, (301) 496-9151.
For information on parking and other matters, call Angela Martin, (301) 496-2535.
Coffee will be served before the program.

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[*] *Chromatin, a complex of DNA and proteins, controls genetic expression by carrying information for the manufacture of proteins, and for the regulation of that process in cellular differentiation. Current research on chromatin and protein synthesis will be presented.*

Editors of publications may request a glossy print of the numbered photographs that appear in this issue.

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